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(54) Title: COMPOSITIONS AND METHODS FOR TREATING BONE DEFICIT CONDITIONS

(57) Abstract

Compounds containing two aromatic systems covalently linked through a linker containing one or more atoms, or "linker" defined as including a covalent bond *per se* so as to space the aromatic systems at a distance 1.5–15Å, are effective in treating conditions associated with bone deficits. The compounds can be administered to vertebrate subjects alone or in combination with additional agents that promote bone growth or that inhibit bone resorption. They can be screened for activity prior to administration by assessing their ability to effect the transcription of a reporter gene coupled to a promoter associated with a bone morphogenetic protein and/or their ability to stimulate calvarial growth in model animal systems.

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COMPOSITIONS AND METHODS FOR TREATING BONE DEFICIT CONDITIONS

Technical Field

The invention relates to compositions and methods for use in limiting undesired bone loss in a vertebrate at risk of such bone loss, in treating conditions that are characterized by undesired bone loss or by the need for bone growth, in treating fractures, and in treating cartilage disorders. More specifically, the invention concerns the use of specific classes of compounds identified or characterized by a high throughput screening assay.

Background Art

Bone is not a static tissue. It is subject to constant breakdown and resynthesis in a complex process mediated by osteoblasts, which produce new bone, and osteoclasts, which destroy bone. The activities of these cells are regulated by a large number of cytokines and growth factors, many of which have now been identified and cloned. Mundy has described the current knowledge related to these factors (Mundy, G.R. *Clin Orthop* 324:24-28, 1996; Mundy, G.R. *J Bone Miner Res* 8:S505-10, 1993).

Although there is a great deal of information available on the factors which influence the breakdown and resorption of bone, information on growth factors which stimulate the formation of new bone is more limited. Investigators have searched for sources of such activities, and have found that bone tissue itself is a storehouse for factors which have the capacity for stimulating bone cells. Thus, extracts of bovine bone tissue obtained from slaughterhouses contain not only structural proteins which are responsible for maintaining the structural integrity of bone, but also biologically active bone growth factors which can stimulate bone cells to proliferate. Among these latter factors are transforming growth factor ß, the heparin-binding growth factors (acidic and basic fibroblast growth factor), the insulin-like growth factors (insulin-like growth factor I and insulin-like growth factor II), and a recently described family of

proteins called bone morphogenetic proteins (BMPs). All of these growth factors have effects on other types of cells, as well as on bone cells.

The BMPs are novel factors in the extended transforming growth factor ß superfamily. They were first identified by Wozney J. *et al. Science* (1988) 242:1528-34, using gene cloning techniques, following earlier descriptions characterizing the biological activity in extracts of demineralized bone (Urist M. *Science* (1965) 150:893-99). Recombinant BMP2 and BMP4 can induce new bone formation when they are injected locally into the subcutaneous tissues of rats (Wozney J. *Molec Reprod Dev* (1992) 32:160-67). These factors are expressed by normal osteoblasts as they differentiate, and have been shown to stimulate osteoblast differentiation and bone nodule formation *in vitro* as well as bone formation *in vivo* (Harris S. *et al. J. Bone Miner Res* (1994) 9:855-63). This latter property suggests potential usefulness as therapeutic agents in diseases which result in bone loss.

The cells which are responsible for forming bone are osteoblasts. As osteoblasts differentiate from precursors to mature bone-forming cells, they express and secrete a number of enzymes and structural proteins of the bone matrix, including Type-1 collagen, osteocalcin, osteopontin and alkaline phosphatase (Stein G. *et al. Curr Opin Cell Biol* (1990) 2:1018-27; Harris S. *et al.* (1994), *supra*). They also synthesize a number of growth regulatory peptides which are stored in the bone matrix, and are presumably responsible for normal bone formation. These growth regulatory peptides include the BMPs (Harris S. *et al.* (1994), *supra*). In studies of primary cultures of fetal rat calvarial osteoblasts, BMPs 1, 2, 3, 4, and 6 are expressed by cultured cells prior to the formation of mineralized bone nodules (Harris S. *et al.* (1994), *supra*). Like alkaline phosphatase, osteocalcin and osteopontin, the BMPs are expressed by cultured osteoblasts as they proliferate and differentiate.

Although the BMPs are potent stimulators of bone formation *in vitro* and *in vivo*, there are disadvantages to their use as therapeutic agents to enhance bone healing. Receptors for the bone morphogenetic proteins have been identified in many tissues, and the BMPs themselves are expressed in a large variety of tissues in specific temporal and spatial patterns. This suggests that BMPs may have effects on many

tissues other than bone, potentially limiting their usefulness as therapeutic agents when administered systemically. Moreover, since they are peptides, they would have to be administered by injection. These disadvantages impose severe limitations to the development of BMPs as therapeutic agents.

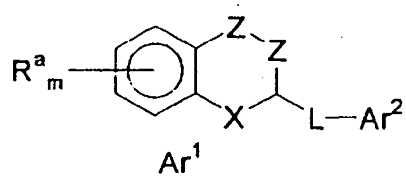
There is a plethora of conditions which are characterized by the need to enhance bone formation. Perhaps the most obvious is the case of bone fractures, where it would be desirable to stimulate bone growth and to hasten and complete bone repair. Agents that enhance bone formation would also be useful in facial reconstruction procedures. Other bone deficit conditions include bone segmental defects, periodontal disease, metastatic bone disease, osteolytic bone disease and conditions where connective tissue repair would be beneficial, such as healing or regeneration of cartilage defects or injury. Also of great significance is the chronic condition of osteoporosis, including age-related osteoporosis and osteoporosis associated with postmenopausal hormone status. Other conditions characterized by the need for bone growth include primary and secondary hyperparathyroidism, disuse osteoporosis, diabetes-related osteoporosis, and glucocorticoid-related osteoporosis. In addition, or alternatively, the compounds of the present invention may modulate metabolism, proliferation and/or differentiation of normal or aberrant cells or tissues.

There are currently no satisfactory pharmaceutical approaches to managing any of these conditions. Bone fractures are still treated exclusively using casts, braces, anchoring devices and other strictly mechanical means. Further bone deterioration associated with postmenopausal osteoporosis has been decreased or prevented with estrogens or bisphosphonates.

US Patent 5, 280, 040 discloses a class of compounds which are 3, 4-diaryl chromans. These compounds can be considered derivatives of 2,3,4 triphenyl butanol, where the hydroxy at the 1-position forms an ether with the ortho position of the phenyl group substituted at the 4-position of the butanol. The parent 3,4-diaryl chromans do not contain nitrogen atoms in the aromatic moieties or their linkers. A preferred compound, centchroman, contains a nitrogen substituent only in one of the

substituents on a phenyl moiety. These compounds are disclosed in the '040 patent as useful in the treatment of osteoporosis.

In addition, the PCT application WO97/15308 published 1 May 1997 describes a number of classes of compounds that are active in the screening assay described below and are useful in treating bone disorders. These compounds, generically, are of the formulae



wherein R^a is a non-interfering substituent;

m is an integer of 0-4;

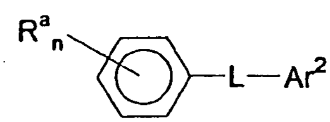
each dotted line represents an optional π-bond;

each Z is independently N, NR, O, S, CR or CR_2, where each R is independently H or alkyl (1-6C);

X is O, S, SO or SO_2;

L is a flexible linker; and

Ar^2 is a substituted or unsubstituted 6-membered aromatic ring; or:



wherein R^a is a non-interfering substituent;

n is an integer of 0 and 5;

L is a flexible linker which does not contain nitrogen or is a constrained linker; and

Ar^2 is a substituted or unsubstituted phenyl or a substituted or unsubstituted naphthyl.

There remains a need for additional compositions which can ameliorate the effects of abnormalities in bone formation or resorption. The present invention

expands the repertoire of compounds useful for limiting or treating bone deficit conditions, and for other uses that should be apparent to those skilled in the art from the teachings herein.

Disclosure of the Invention

The invention provides compounds that can be administered as ordinary pharmaceuticals and have the metabolic effect of enhancing bone growth or inhibiting resorption. The compounds of the invention can be identified using an assay for their ability to activate control elements associated with bone anabolic factors. Thus, the invention is directed to methods and compositions for treating bone disorders, which methods and compositions use, as active ingredients, compounds wherein two aromatic systems are coupled so as to be spaced apart from each other by about 1.5 to about 15 Angstroms. The thus-linked systems (including the linker coupling them) preferably include at least one nitrogen atom.

Therefore, the compounds useful in the invention can be described as having the formula Ar^1-linker-Ar^2, wherein each of Ar^1 and Ar^2 is independently an aromatic system and the linker portion of the formula spaces Ar^1 and Ar^2 apart by a distance of approximately 1.5-15 Angstroms. Ar^1, Ar^2 and the linker may optionally be substituted with non interfering substituents. In the useful compounds, there is preferably at least one nitrogen atom in either Ar^1, Ar^2 and/or the linker, independent of any substituents thereon. Preferably, the compounds of the invention contain at least one additional heteroatom selected from the group consisting of N, S and O, independent of any substituent.

Thus, in one aspect, the invention is directed to a method to treat a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth replacement and/or an undesirable level of bone resorption, which method comprises administering to a vertebrate subject in need of such treatment an effective amount of certain compounds of the formula:

$$Ar^1\text{-}L\text{-}Ar^2$$

wherein each of Ar^1 and Ar^2 is independently substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, a substituted or unsubstituted aromatic system containing a 6-membered heterocycle, or a substituted or unsubstituted aromatic system containing a 5-membered heterocycle; and

L is a linker that provides spacing of 1.5-15Å.

In other aspects, the invention relates to pharmaceutical compositions for use in the method, and to the compounds for use in preparing a medicament for use in the method.

Brief Description of the Drawings

Figure 1 gives a schematic representation of the compounds used as active ingredients in the methods and compositions of the invention.

Figure 2 shows the dose response curve for a positive control compound, designated 59-0008.

Figures 3 and 4 show illustrative compounds of the invention and the results obtained with them in an *in vitro* test for stimulation of bone growth.

Figures 5A, 5B and 5C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0072.

Figures 6A, 6B and 6C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 50-0197.

Figure 7 shows structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0145.

Figures 8A, 8B and 8C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0045.

Figure 9 shows the results in an *ex vivo* calvarial assay for various compunds of the invention.

Figure 10 shows the increase in bone volume effected by subcutaneous administration of compound 59-0145 in the OVX *in vivo* assay.

Figure 11 is a graphical representation of percent increase in trabecular bone in ovariectomized rats treated with compound 59-0145.

Figure 12 presents graphs showing results of qCT and bone histomorphometri and serum osteocalcin levels in rats treated with compound 59-0145.

Figure 13 (41 pages) is a list of compounds used in screening for bone morphogenic activity according to the screening assay set forth herein.

Modes of Carrying Out the Invention

A rapid throughput screening test for compounds capable of stimulating expression of a reporter gene linked to a BMP promoter (a surrogate for the production of bone morphogenetic factors that are endogenously produced) is described in WO96/38590 published 5 December 1996, the contents of which are incorporated herein by reference. This assay is also described as a portion of a study of immortalized murine osteoblasts (derived from a mouse expressing a transgene composed of a BMP2 promoter driving expression of T-antigen) in Ghosh-Choudhery, N. *et al. Endocrinology* (1996) 137:331-39. In this study, the immortalized cells were stably transfected with a plasmid containing a luciferase reporter gene driven by a mouse BMP2 promoter (-2736/114 bp), and responded in a dose-dependent manner to recombinant human BMP2.

Briefly, the assay utilizes cells transformed permanently or transiently with constructs in which the promoter of a bone morphogenetic protein, specifically BMP2 or BMP4, is coupled to a reporter gene, typically luciferase. These transformed cells are then evaluated for the production of the reporter gene product; compounds that activate the BMP promoter will drive production of the reporter protein, which can be readily assayed. Over 40,000 compounds have been subjected to this rapid screening technique, and only a very small percentage are able to elicit a level of production of luciferase 5-fold greater than that produced by vehicle. Compounds that activate the BMP promoter share certain structural characteristics not present in inactive compounds. The active compounds ("BMP promoter-active compounds" or "active compounds") are useful in promoting bone or cartilage growth, and thus in the treatment of vertebrates in need of bone or cartilage growth.

BMP promoter-active compounds can be examined in a variety of other assays that test specificity and toxicity. For instance, nonBMP promoters or response elements can be linked to a reporter gene and inserted into an appropriate host cell. Cytotoxicity can be determined by visual or microscopic examination of BMP promoter- and/or nonBMP promoter-reporter gene-containing cells, for instance. Alternatively, nucleic acid and/or protein synthesis by the cells can be monitored. For *in vivo* assays, tissues may be removed and examined visually or microscopically, and optionally examined in conjunction with dyes or stains that facilitate histologic examination. In assessing *in vivo* assay results, it may also be useful to examine biodistribution of the test compound, using conventional medicinal chemistry/animal model techniques.

As used herein, "limit" or "limiting" and "treat" or "treatment" are interchangeable terms. The terms include a postponement of development of bone deficit symptoms and/or a reduction in the severity of such symptoms that will or are expected to develop. The terms further include ameliorating existing bone or cartilage deficit symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, preventing or reversing bone resorption and/or encouraging bone growth. Thus, the terms denote that a beneficial result has been conferred on a vertebrate subject with a cartilage, bone or skeletal deficit, or with the potential to develop such deficit.

By "bone deficit" is meant an imbalance in the ratio of bone formation to bone resorption, such that, if unmodified, the subject will exhibit less bone than desirable, or the subject's bones will be less intact and coherent than desired. Bone deficit may also result from fracture, from surgical intervention or from dental or periodontal disease. By "cartilage defect" is meant damaged cartilage, less cartilage than desired, or cartilage that is less intact and coherent than desired.

Representative uses of the compounds of the present invention include: repair of bone defects and deficiencies, such as those occuring in closed, open and nonunion fractures; prophylactic use in closed and open fracture reduction; promotion of bone healing in plastic surgery; stimulation of bone ingrowth into noncemented prosthetic

joints and dental implants; elevation of peak bone mass in premenopausal women; treatment of growth deficiencies; treatment of peridontal disease and defects, and other tooth repair processes; increase in bone formation during distraction osteogenesis; and treatment of other skeletal disorders, such as age-related osteoporosis, postmenopausal osteoporosis, glucocorticoid-induced osteoporosis or disuse osteoporosis and arthritis. The compounds of the present invention can also be useful in repair of congenital, trauma-induced or surgical resection of bone (for instance, for cancer treatment), and in cosmetic surgery. Further, the compounds of the present invention can be used for limiting or treating cartilage defects or disorders, and may be useful in wound healing or tissue repair.

Bone or cartilage deficit or defect can be treated in vertebrate subjects by administering compounds of the invention which have been identified through suitable screening assays and which exhibit certain structural characteristics. The compositions of the invention may be administered systemically or locally. For systemic use, the compounds herein are formulated for parenteral (e.g., intravenous, subcutaneous, intramuscular, intraperitoneal, intranasal or transdermal) or enteral (e.g., oral or rectal) delivery according to conventional methods. Intravenous administration will be by a series of injections or by continuous infusion over an extended period. Administration by injection or other routes of discretely spaced administration will generally be performed at intervals ranging from weekly to once to three times daily. Alternatively, the compounds disclosed herein may be administered in a cyclical manner (administration of disclosed compound; followed by no administration; followed by administration of disclosed compound, and the like). Treatment will continue until the desired outcome is achieved. In general, pharmaceutical formulations will include a compound of the present invention in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water, borate-buffered saline containing trace metals or the like. Formulations may further include one or more excipients, preservatives, solubilizers, buffering agents, albumin to prevent protein loss on vial surfaces, lubricants, fillers, stabilizers, etc. Methods of formulation are well known in the art and are disclosed, for example, in Remington's Pharmaceutical

Sciences, Gennaro, ed., Mack Publishing Co., Easton PA, 1990, which is incorporated herein by reference. Pharmaceutical compositions for use within the present invention can be in the form of sterile, nonpyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms known in the art. Local administration may be by injection at the site of injury or defect, or by insertion or attachment of a solid carrier at the site, or by direct, topical application of a viscous liquid. For local administration, the delivery vehicle preferably provides a matrix for the growing bone or cartilage, and more preferably is a vehicle that can be absorbed by the subject without adverse effects.

Delivery of compounds herein to wound sites may be enhanced by the use of controlled-release compositions, such as those described in WIPO publication WO 93/20859, which is incorporated herein by reference in its entirety. Films of this type are particularly useful as coatings for prosthetic devices and surgical implants. The films may, for example, be wrapped around the outer surfaces of surgical screws, rods, pins, plates and the like. Implantable devices of this type are routinely used in orthopedic surgery. The films can also be used to coat bone filling materials, such as hydroxyapatite blocks, demineralized bone matrix plugs, collagen matrices and the like. In general, a film or device as described herein is applied to the bone at the fracture site. Application is generally by implantation into the bone or attachment to the surface using standard surgical procedures.

In addition to the copolymers and carriers noted above, the biodegradable films and matrices may include other active or inert components. Of particular interest are those agents that promote tissue growth or infiltration, such as growth factors. Exemplary growth factors for this purpose include epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factors (TGFs), parathyroid hormone (PTH), leukemia inhibitory factor (LIF), and insulin-like growth factors (IGFs). Agents that promote bone growth, such as bone morphogenetic proteins (U.S. Patent No. 4,761,471; PCT Publication WO 90/11366), osteogenin (Sampath *et al. Proc. Natl. Acad. Sci. USA* (1987) 84:7109-13) and NaF (Tencer *et al. J. Biomed. Mat. Res.* (1989) 23: 571-89) are also preferred.

Biodegradable films or matrices include calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyanhydrides, bone or dermal collagen, pure proteins, extracellular matrix components and combinations thereof. Such biodegradable materials may be used in combination with nonbiodegradable materials, to provide desired mechanical, cosmetic or tissue or matrix interface properties.

Alternative methods for delivery of compounds of the present invention include use of ALZET osmotic minipumps (Alza Corp., Palo Alto, CA); sustained release matrix materials such as those disclosed in Wang *et al.* (PCT Publication WO 90/11366); electrically charged dextran beads, as disclosed in Bao *et al.* (PCT Publication WO 92/03125); collagen-based delivery systems, for example, as disclosed in Ksander *et al. Ann. Surg.* (1990) 211(3):288-94; methylcellulose gel systems, as disclosed in Beck *et al. J. Bone Min. Res.* (1991) 6(11):1257-65; and alginate-based systems, as disclosed in Edelman *et al. Biomaterials* (1991) 12:619-26. Other methods well known in the art for sustained local delivery in bone include porous coated metal protheses that can be impregnated and solid plastic rods with therapeutic compositions incorporated within them.

The compounds of the present invention may also be used in conjunction with agents that inhibit bone resorption. Antiresorptive agents, such as estrogen, bisphosphonates and calcitonin, are preferred for this purpose. More specifically, the compounds disclosed herein may be administered for a period of time (for instance, months to years) sufficient to obtain correction of a bone deficit condition. Once the bone deficit condition has been corrected, the vertebrate can be administered an anti-resorptive compound to maintain the corrected bone condition. Alternatively, the compounds disclosed herein may be adminstered with an anti-resorptive compound in a cyclical manner (administration of disclosed compound, followed by anti-resorptive, followed by disclosed compound, and the like).

In additional formulations, conventional preparations such as those described below may be used.

Aqueous suspensions may contain the active ingredient in admixture with pharmacologically acceptable excipients, comprising suspending agents, such as methyl

cellulose; and wetting agents, such as lecithin, lysolethicin or long-chain fatty alcohols. The said aqueous suspensions may also contain preservatives, coloring agents, flavoring agents and sweetening agents in accordance with industry standards.

Preparations for topical and local application comprise aerosol sprays, lotions, gels and ointments in pharmaceutically appropriate vehicles which may comprise lower aliphatic alcohols, polyglycols such as glycerol, polyethylene glycol, esters of fatty acids, oils and fats, and silicones. The preparations may further comprise antioxidants, such as ascorbic acid or tocopherol, and preservatives, such as p-hydroxybenzoic acid esters.

Parenteral preparations comprise particularly sterile or sterilized products. Injectable compositions may be provided containing the active compound and any of the well known injectable carriers. These may contain salts for regulating the osmotic pressure.

If desired, the osteogenic agents can be incorporated into liposomes by any of the reported methods of preparing liposomes for use in treating various pathogenic conditions. The present compositions may utilize the compounds noted above incorporated in liposomes in order to direct these compounds to macrophages, monocytes, other cells and tissues and organs which take up the liposomal composition. The liposome-incorporated compounds of the invention can be utilized by parenteral administration, to allow for the efficacious use of lower doses of the compounds. Ligands may also be incorporated to further focus the specificity of the liposomes.

Suitable conventional methods of liposome preparation include, but are not limited to, those disclosed by Bangham, A.D. *et al. J Mol Biol* (1965) 23:238-252, Olson, F. *et al. Biochim Biophys Acta* (1979) 557:9-23, Szoka, F. *et al. Proc Natl Acad Sci USA* (1978) 75:4194-4198, Mayhew, E. *et al.* _________ (1984) 775:169-175, Kim, S. *et al. Biochim Biophys Acta* (1983) 728:339:348, and Mayer, *et al. Biochim Biophys Acta* (1986) 858:161-16°.

The liposomes may be made from the present compounds in combination with any of the conventional synthetic or natural phospholipid liposome materials including

phospholipids from natural sources such as egg, plant or animal sources such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, sphingomyelin, phosphatidylserine, or phosphatidylinositol. Synthetic phospholipids that may also be used, include, but are not limited to: dimyristoylphosphatidylcholine, dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidycholine, and the corresponding synthetic phosphatidylethanolamines and phosphatidylglycerols. Cholesterol or other sterols, cholesterol hemisuccinate, glycolipids, cerebrosides, fatty acids, gangliosides, sphingolipids, 1,2-bis(oleoyloxy)-3-(trimethyl ammonio) propane (DOTAP), N-[1-(2,3-dioleoyl) propyl-N,N,N-trimethylammonium chloride (DOTMA), and other cationic lipids may be incorporated into the liposomes, as is known to those skilled in the art. The relative amounts of phospholipid and additives used in the liposomes may be varied if desired. The preferred ranges are from about 60 to 90 mole percent of the phospholipid; cholesterol, cholesterol hemisuccinate, fatty acids or cationic lipids may be used in amounts ranging from 0 to 50 mole percent. The amounts of the present compounds incorporated into the lipid layer of liposomes can be varied with the concentration of their lipids ranging from about 0.01 to about 50 mole percent.

Using conventional methods, approximately 20 to 30% of the compound present in solution can be entrapped in liposomes; thus, approximately 70 to 80% of the active compound is wasted. In contrast, where the compound is incorporated into liposomes, virtually all of the compound is incorporated into the liposome, and essentially none of the active compound is wasted.

The liposomes with the above formulations may be made still more specific for their intended targets with the incorporation of monoclonal antibodies or other ligands specific for a target. For example, monoclonal antibodies to the BMP receptor may be incorporated into the liposome by linkage to phosphatidylethanolamine (PE) incorporated into the liposome by the method of Leserman, L. *et al. Nature* (1980) 288:602-604.

Veterinary uses of the disclosed compounds are also contemplated. Such uses would include limitation or treatment of bone or cartilage deficits or defects in

domestic animals, livestock and thoroughbred horses. The compounds described herein can also modify a target tissue or organ environment, so as to attract bone-forming cells to an environment in need of such cells.

The compounds of the present invention may also be used to stimulate growth of bone-forming cells or their precursors, or to induce differentiation of bone-forming cell precursors, either *in vitro* or ex vivo. As used herein, the term "precursor cell" refers to a cell that is committed to a differentiation pathway, but that generally does not express markers or function as a mature, fully differentiated cell. As used herein, the term "mesenchymal cells" or "mesenchymal stem cells" refers to pluripotent progenitor cells that are capable of dividing many times, and whose progeny will give rise to skeletal tissues, including cartilage, bone, tendon, ligament, marrow stroma and connective tissue (see A. Caplan *J. Orthop. Res.* (1991) 9:641-50). As used herein, the term "osteogenic cells" includes osteoblasts and osteoblast precursor cells. More particularly, the disclosed compounds are useful for stimulating a cell population containing marrow mesenchymal cells, thereby increasing the number of osteogenic cells in that cell population. In a preferred method, hematopoietic cells are removed from the cell population, either before or after stimulation with the disclosed compounds. Through practice of such methods, osteogenic cells may be expanded. The expanded osteogenic cells can be infused (or reinfused) into a vertebrate subject in need thereof. For instance, a subject's own mesenchymal stem cells can be exposed to compounds of the present invention ex vivo, and the resultant osteogenic cells could be infused or directed to a desired site within the subject, where further proliferation and/or differentiation of the osteogenic cells can occur without immunorejection. Alternatively, the cell population exposed to the disclosed compounds may be immortalized human fetal osteoblastic or osteogenic cells. If such cells are infused or implanted in a vertebrate subject, it may be advantageous to "immunoprotect" these nonself cells, or to immunosuppress (preferably locally) the recipient to enhance transplantation and bone or cartilage repair.

Within the present invention, an "effective amount" of a composition is that amount which produces a statistically significant effect. For example, an "effective

amount" for therapeutic uses is the amount of the composition comprising an active compound herein required to provide a clinically significant increase in healing rates in fracture repair; reversal of bone loss in osteoporosis; reversal of cartilage defects or disorders; prevention or delay of onset of osteoporosis; stimulation and/or augmentation of bone formation in fracture nonunions and distraction osteogenesis; increase and/or acceleration of bone growth into prosthetic devices; and repair of dental defects. Such effective amounts will be determined using routine optimization techniques and are dependent on the particular condition to be treated, the condition of the patient, the route of administration, the formulation, and the judgment of the practitioner and other factors evident to those skilled in the art. The dosage required for the compounds of the invention (for example, in osteoporosis where an increase in bone formation is desired) is manifested as a statistically significant difference in bone mass between treatment and control groups. This difference in bone mass may be seen, for example, as a 5-20% or more increase in bone mass in the treatment group. Other measurements of clinically significant increases in healing may include, for example, tests for breaking strength and tension, breaking strength and torsion, 4-point bending, increased connectivity in bone biopsies and other biomechanical tests well known to those skilled in the art. General guidance for treatment regimens is obtained from experiments carried out in animal models of the disease of interest.

The dosage of the compounds of the invention will vary according to the extent and severity of the need for treatment, the activity of the administered compound, the general health of the subject, and other considerations well known to the skilled artisan. Generally, they can be administered to a typical human on a daily basis on an oral dose of about 0.1 mg/kg-1000 mg/kg, and more preferably from about 1 mg/kg to about 200 mg/kg. The parenteral dose will appropriately be 20-100% of the oral dose.

Screening Assays

The osteogenic activity of the compounds used in the methods of the invention can be verified using *in vitro* screening techniques, such as the assessment of

transcription of a reporter gene coupled to a bone morphogenetic protein-associated promoter, as described above, or in alternative assays such as the following:

Technique for Neonatal Mouse Calvarial Assay (*In vitro*)

This assay is similar to that described by Gowen M. & Mundy G. *J Immunol* (1986) 136:2478-82. Briefly, four days after birth, the front and parietal bones of ICR Swiss white mouse pups are removed by microdissection and split along the sagittal suture. The bones are incubated in BGJb medium (Irvine Scientific, Santa Ana, CA) plus 0.02% (or lower concentration) β-methylcyclodextrin, wherein the medium also contains test or control substances, at 37°C in a humidified atmosphere of 5% CO_2 and 95% air for 96 hours.

Following this, the bones are removed from the incubation media and fixed in 10% buffered formalin for 24-48 hours, decalcified in 14% EDTA for 1 week, processed through graded alcohols; and embedded in paraffin wax. Three μm sections of the calvaria are prepared. Representative sections are selected for histomorphometric assessment of bone formation and bone resorption. Bone changes are measured on sections cut 200 μm apart. Osteoblasts and osteoclasts are identified by their distinctive morphology.

Other auxillary assays can be used as controls to determine nonBMP promoter-mediated effects of test compounds. For example, mitogenic activity can be measured using screening assays featuring a serum-response element (SRE) as a promoter and a luciferase reporter gene. More specifically, these screening assays can detect signalling through SRE-mediated pathways, such as the protein kinase C pathway. For instance, an osteoblast activator SRE-luciferase screen and an insulin mimetic SRE-luciferase screen are useful for this purpose. Similarly, test compound stimulation of cAMP response element (CRE)-mediated pathways can also be assayed. For instance, cells transfected with receptors for PTH and calcitonin (two bone-active agents) can be used in CRE-luciferase screens to detect elevated cAMP levels. Thus, the BMP promoter specificity of a test compound can be examined through use of these types of auxillary assays.

In vivo Assay of Effects of Compounds on Murine Calvarial Bone Growth

Male ICR Swiss white mice, aged 4-6 weeks and weighing 13-26 gm, are employed, using 4-5 mice per group. The calvarial bone growth assay is performed as described in PCT application WO 95/24211. Briefly, the test compound or appropriate control vehicle is injected into the subcutaneous tissue over the right calvaria of normal mice. Typically, the control vehicle is the vehicle in which the compound was solubilized, and is PBS containing 5% DMSO or is PBS containing Tween (2 µl/10 ml). The animals are sacrificed on day 14 and bone growth measured by histomorphometry. Bone samples for quantitation are cleaned from adjacent tissues and fixed in 10% buffered formalin for 24-48 hours, decalcified in 14% EDTA for 1-3 weeks, processed through graded alcohols; and embedded in paraffin wax. Three to five µm sections of the calvaria are prepared, and representative sections are selected for histomorphometric assessment of the effects on bone formation and bone resorption. Sections are measured by using a camera lucida attachment to trace directly the microscopic image onto a digitizing plate. Bone changes are measured on sections cut 200 µm apart, over 4 adjacent 1x1 mm fields on both the injected and noninjected sides of the calvaria. New bone is identified by its characteristic woven structure, and osteoclasts and osteoblasts are identified by their distinctive morphology. Histomorphometry software (OsteoMeasure, Osteometrix, Inc., Atlanta) is used to process digitizer input to determine cell counts and measure areas or perimeters.

Additional *In Vivo* Assays

Lead compounds can be further tested in intact animals using an *in vivo*, dosing assay. Prototypical dosing may be accomplished by subcutaneous, intraperitoneal or oral administration, and may be performed by injection, sustained release or other delivery techniques. The time period for administration of test compound may vary (for instance, 28 days as well as 35 days may be appropriate). An exemplary, *in vivo* subcutaneous dosing assay may be conducted as follows:

In a typical study, 70 three-month-old female Sprague-Dawley rats are weight-matched and divided into seven groups, with ten animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; a control group administered vehicle only; a PBS-treated control group; and a positive control group administered a compound (nonprotein or protein) known to promote bone growth. Three dosage levels of the compound to be tested are administered to the remaining three groups.

Briefly, test compound, positive control compound, PBS, or vehicle alone is administered subcutaneously once per day for 35 days. All animals are injected with calcein nine days and two days before sacrifice (two injections of calcein administered each designated day). Weekly body weights are determined. At the end of the 35-day cycle, the animals are weighed and bled by orbital or cardiac puncture. Serum calcium, phosphate, osteocalcin, and CBCs are determined. Both leg bones (femur and tibia) and lumbar vertebrae are removed, cleaned of adhering soft tissue, and stored in 70% ethanol for evaluation, as performed by peripheral quantitative computed tomography (pqCT; Ferretti, J. *Bone* (1995) 17:353S-64S), dual energy X-ray absorptiometry (DEXA; Laval-Jeantet A. *et al. Calcif Tissue Intl* (1995) 56:14-18; J. Casez *et al. Bone and Mineral* (1994) 26:61-68) and/or histomorphometry. The effect of test compounds on bone remodeling can thus be evaluated.

Lead compounds also be tested in acute ovariectomized animals (prevention model) using an *in vivo* dosing assay. Such assays may also include an estrogen-treated group as a control. An exemplary subcutaneous dosing assay is performed as follows:

In a typical study, 80 three-month-old female Sprague-Dawley rats are weight-matched and divided into eight groups, with ten animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; three control groups (sham ovariectomized (sham OVX) + vehicle only; ovariectomized (OVX) + vehicle only; PBS-treated OVX); and a control OVX group that is administered a compound known to promote bone growth. Three dosage levels of the compound to be tested are administered to the remaining three groups of OVX animals.

Since ovariectomy (OVX) induces hyperphagia, all OVX animals are pair-fed with sham OVX animals throughout the 35 day study. Briefly, test compound, positive control compound, PBS, or vehicle alone is administered subcutaneously once per day for 35 days. Alternatively, test compound can be formulated in implantable pellets that are implanted for 35 days, or may be administered orally, such as by gastric gavage. All animals, including sham OVX/vehicle and OVX/vehicle groups, are injected intraperitoneally with calcein nine days and two days before sacrifice (two injections of calcein administered each designated day, to ensure proper labeling of newly formed bone). Weekly body weights are determined. At the end of the 35-day cycle, the animals' blood and tissues are processed as described above.

Lead compounds may also be tested in chronic OVX animals (treatment model). An exemplary protocol for treatment of established bone loss in ovariectomized animals that can be used to assess efficacy of anabolic agents may be performed as follows. Briefly, 80 to 100 six month old female, Sprague-Dawley rats are subjected to sham surgery (sham OVX) or ovariectomy (OVX) at time 0, and 10 rats are sacrificed to serve as baseline controls. Body weights are recorded weekly during the experiment. After approximately 6 weeks of bone depletion (42 days), 10 sham OVX and 10 OVX rats are randomly selected for sacrifice as depletion period controls. Of the remaining animals, 10 sham OVX and 10 OVX rats are used as placebo-treated controls. The remaining OVX animals are treated with 3 to 5 doses of test drug for a period of 5 weeks (35 days). As a postitive control, a group of OVX rats can be treated with an agent such as PTH, a known anabolic agent in this model (Kimmel *et al. Endocrinology* (1993) 132:1577-84). To determine effects on bone formation, the following procedure can be followed. The femurs, tibiae and lumbar vertebrae 1 to 4 are excised and collected. The proximal left and right tibiae are used for pqCT measurements, cancellous bone mineral density (BMD) (gravimetric determination), and histology, while the midshaft of each tibiae is subjected to cortical BMD or histology. The femurs are prepared for pqCT scanning of the midshaft prior to biomechanical testing. With respect to lumbar vertebrae (LV), LV2 are processed

for BMD (pqCT may also be performed); LV3 are prepared for undecalcified bone histology; and LV4 are processed for mechanical testing.

Nature of the Compounds Useful in the Invention

All of the compounds of the invention contain two aromatic systems, Ar^1 and Ar^2, spaced apart by a linker at a distance of 1.5-15Å, and may preferably contain at least one nitrogen atom. A summary of the structural features of the compounds included within the invention is shown in Figure 1.

As shown, Ar^1 and Ar^2 may include various preferred embodiments. These are selected from the group consisting of a substituted or unsubstituted aromatic ring system containing a 5-membered heterocycle; a substituted or unsubstituted aromatic ring system containing a six-membered heterocycle; a substituted or unsubstituted naphthalene moiety; and a substituted or unsubstituted benzene moiety. There are 16 possible combinations of these embodiments, if Ar^1 and Ar^2 are considered distinguishable. As will be clear, however, the designation of one aromatic system as Ar^1 and the other as Ar^2 is arbitrary; thus there are only ten possible combinations. However, for simplicity, Ar^1 and Ar^2 are designated separately with the realization that the choice is arbitrarily made. All linkers described herein if not palindromic, are considered to link Ar^1 to Ar^2 or *vice-versa* whether or not the complementary orientation is explicitly shown (as it is in some cases). Thus, if Ar^1 and Ar^2 are different and a linker is specified as -CONR-, it is understood that also included is the linker -NRCO- when the designations Ar^1 and Ar^2 are retained.

The noninterfering substituents on the aromatic system represented by Ar^1 and the noninterfering substituents on the aromatic system represented by Ar^2 are represented in the formulas herein by R^a and R^b, respectively. Generally, these substituents can be of wide variety. Among substituents that do not interfere with (and in some instances may be desirable for) the beneficial effect of the compounds of the invention on bone in treated subjects are included alkyl (1-6C, preferably lower alkyl 1-4C), including straight or branched-chain forms thereof, alkenyl (1-6C, preferably 1-4C), alkynyl (1-6C, preferably 1-4C), all of which can be straight or branched chains

or are aryl (6-10C) or alkylaryl (6-15C) or aryl alkyl (6-15C) and may contain further substituents. R^a and R^b may also include halogens, (e.g. F, Cl, Br and I); siloxy, OR, SR, NR_2, OOCR, COOR, NCOR, NCOOR, and benzoyl, CF_3, OCF_3, SCF_3, $N(CF_3)_2$, NO, NO_2, CN, SO, SO_2R, SO_3R and the like, wherein R is alkyl (1-6C) or is H. Similarly, these substituents may contain R' as a substitute for R wherein R' is aryl (6-10C) or alkylaryl (6-15C) or aryl alkyl (6-15C). Where R^a or R^b substituents are in adjacent positions in the aromatic system, they may combine to form a ring. Further, rings may be included in substituents which contain sufficient carbon and heteroatoms to provide this possibility.

The choice of noninterfering substituents depends on the overall nature of the system. For example, in compounds of the invention wherein two pyridine rings are linked through a saturated flexible linker, a CF_3 substituent para to the linker in each of the pyridine rings is particularly preferred. In those systems wherein a quinoline is coupled through a flexible conjugated or nonconjugated linker to a phenyl substituent or to a naphthyl substituent, an amino group para to the linker in the phenyl or naphthyl moiety is preferred. Particularly preferred amino groups are dimethylamino and diethylamino. In systems wherein a benzothiazole is coupled to phenyl through a flexible linker, preferred substituents on the phenyl moiety include alkoxy or alkylthio in combination with halo, in particular, chloro. Also preferred is the presence of a diethylamino group in the phenyl moiety para to the position that is coupled to the linker. In general, the presence of a substituent in the phenyl moiety para to the position of joinder to the linker is preferred.

Generally, preferred noninterfering substituents include hydrocarbyl groups of 1-6C, including saturated and unsaturated, linear or branched hydrocarbyl as well as hydrocarbyl groups containing ring systems; halo groups, alkoxy, hydroxy, amino, monoalkyl- and dialkylamino where the alkyl groups are 1-6C, CN, CF_3, OCF_3 and COOR, and the like.

Although the number of R^a and R^b may typically be 0-4 (m) or 0-5 (n) depending on the available positions in the aromatic system, preferred embodiments

include those wherein the number of R^a is 0, 1 or 2 and of R^b is 0, 1, 2 or 3, particularly 1 or 2.

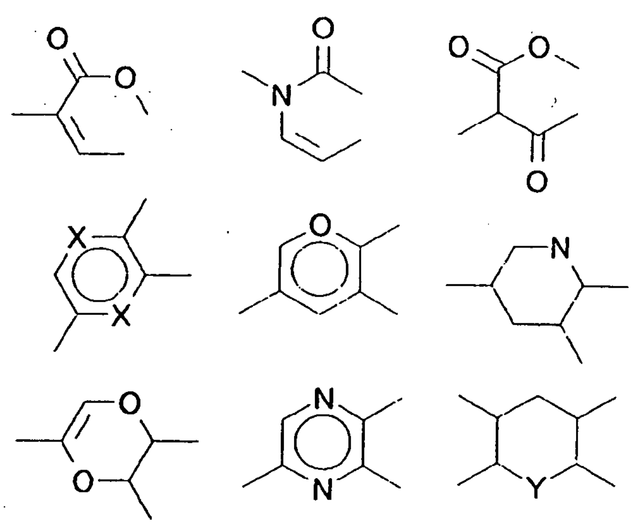
The linker group, L, may be a covalent bond or any group having a valence of at least two and covering a linear distance of from about 1.5 to about 15 Angstroms, including those that contain cyclic moieties, that meet this spatial requirement. Useful linkers are divided, by definition herein, into three general categories: (1) flexible nonconjugating linkers, (2) flexible conjugating linkers, and (3) constrained linkers. The preferred choice of linker will depend on the choices for Ar^1 and Ar^2.

As defined herein, *flexible nonconjugating* linkers are those that link only one position of Ar^1 to one position of Ar^2, and provide only a single covalent bond or a single chain between Ar^1 and Ar^2. The chain may contain branches, but may not contain π-bonds (except in the branches) or cyclic portions in the chain. The linker atoms in the chain itself rotate freely around single covalent bonds, and thus the linker has more than two degrees of freedom. Particularly useful flexible nonconjugating linkers, besides a covalent bond, are those of the formulas: -NR-, $-CR_2-$, -S-, or -O-, wherein R is H or alkyl (1-6C), more preferably H or lower alkyl (1-4C) and more preferably H. Also contemplated are those of the formulas: -NRCO-, -CONR-, $-CR_2S-$, $-SCR_2-$, $-OCR_2-$, $-CR_2O-$, -NRNR-, $-CR_2CR_2-$, $-NRSO_2-$, $-SO_2NR-$, $-CR_2CO-$, $-COCR_2-$, and $-NR-NR-CO-CR_2-$ and its complement $-CR_2-CO-NR-NR-$, or $-NRCR_2CR_2NR-$ or the thiolated counterparts, and particularly $-NHCR_2CR_2NH-$, including the isosteres thereof, such as -NRNRCSNR- and -NRNRCONR-. Also contemplated are those of the formulas: $-NH(CH_2)_2NH-$, $-O(CR_2)_2O-$, and $-S(CR_2)_2S-$, including the isosteres thereof. The optimum choice among flexible nonconjugating linkers is dependent on the nature of Ar^1 and Ar^2.

Flexible conjugating linkers are those that link only one position of Ar^1 to one position of Ar^2, but incorporate at least one double or triple bond or one or more cyclic systems in the chain itself and thus have only two degrees of freedom. A flexible conjugating linker may form a completely conjugated π-bond linking system between Ar^1 and Ar^2, thus providing for co-planarity of Ar^1 and Ar^2. Examples of useful flexible conjugating linkers include: -RC=CR-; -N=N-; -C≡C-; -RC=N-; -N=CR-;

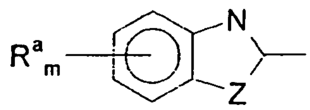
-NR-N=CR-; -NR-NR-CO-CR=CR-, -N=NCOCR$_2$-, -N=NCSCR$_2$-, -N=NCOCR$_2$CR$_2$, -N=NCONR-, -N=NCSNR-, and the like, where R is H or alkyl (1-6C); preferably H or lower alkyl (1-4C); and more preferably H.

Constrained linkers are those that have more than one point of attachment to either or both Ar^1 and Ar^2 and, thus, generally allow for only one degree of freedom. Constrained linkers most frequently form fused 5- or 6-membered cyclic moieties with Ar^1 and/or Ar^2 where either Ar^1 or Ar^2 has at least one substituent appropriately positioned to form a second covalent bond with the linker, e.g., where Ar^2 is a phenyl group with a reactive, ortho-positioned substituent, or is derivatized to the linker directly at the ortho position. (Although the aromatic moieties should properly be referred to as phenylene or naphthylene in such cases, generally the term "phenyl" or "naphthyl" is used herein to include both monovalent and bivalent forms of these moieties.) Examples of particularly useful constrained linkers include



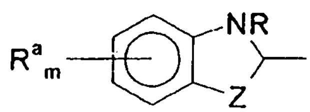
and the like, where X is O, N, S or CR, and Y is CR$_2$ or C=O.

In one class of preferred embodiments, Ar^1 is an aromatic system containing a 5-membered heterocycle, of the formula:



(1a)

or

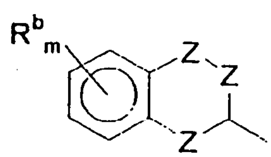


(2a)

wherein Z is S, O, NR or $-CR_2$ in formula (1a) or CR in formula (2a), where each R is independently H or alkyl (1-6C), the dotted line represents an optional π-bond, each R^a is independently a noninterfering substituent as defined above, and m is an integer of 0-4.

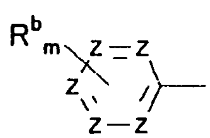
In general, Ar^2 is phenyl, naphthyl, or an aromatic system containing a 5- or 6-membered heterocyclic ring. All may be unsubstituted or substituted with noninterfering substituents, R^b.

When Ar^2 is an aromatic system containing a six-membered heterocycle, the formula of said system is preferably:



(iii)

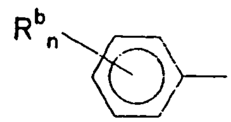
or



(iv)

wherein each Z is independently a heteroatom selected from the group consisting of S, O and N; or is CR or CR_2, the dotted lines represent optional π-bonds, each R^b is independently a noninterfering substituent, and m is an integer of 0-4, with the proviso that at least one Z must be a heteroatom.

Ar^2 in these compounds may also have the formula

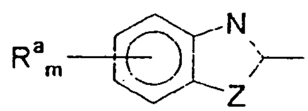


(v)

where R^b is a noninterfering substituent as defined above and n is an integer from 0 to 5.

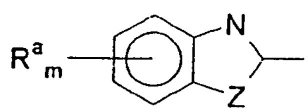
Similarly, when Ar^2 is naphthyl, it may contain 0-5 R^b substitutions. When Ar^2 is an aromatic system containing a 5-membered heterocycle, preferred forms are those as described for Ar^1.

Thus, in one set of preferred compounds, Ar^1 is



(1a)

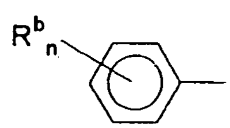
or



(2a)

wherein each R^a is a noninterfering substituent, m is an integer of 0-4, the dotted line represents an optional π bond, and Z is O, S, NR or CR_2 in formula (1) or is CR in formula (2) wherein each R is independently H or alkyl (1-6C).

In one group of these compounds, L is a flexible conjugating or nonconjugating linker. In this group, when Z is NR, Ar^2 is preferably a substituted or unsubstituted aromatic system containing a 5-membered heterocycle or is



(v)

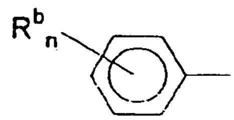
;

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, $-CR_2NR-$, $-CR_2CR_2-$, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or the dotted line represents a π bond.

In these embodiments as well as in alternative embodiments of Ar^2, it is preferred that each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C), or R^b comprises an aromatic system.

Preferred compounds in this group are 59-0100, 59-103, 59-104, 59-105 and 59-106 (See Figure 13).

In another group of these compounds with flexible linkers, Z is S, and Ar^2 is preferably a substituted or unsubstituted aromatic system containing a 6-membered heterocycle or is of the formula



(v)

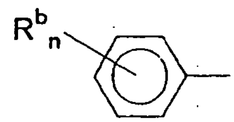
wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, $-CR_2NR-$, $-CR_2CR_2-$, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or the dotted line represents a π bond.

In such compounds, regardless of the choice of Ar^2, preferred are those compounds wherein each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

Both when Z is S and when Z is NR, it is preferred that m is 0 and/or each R^b is independently OR, SR or halo, where n=2 and at least one R^b is independently OR or SR and/or L is -NHCO- or -CR=CR-.

Preferred compounds in this group include compounds 59-002, 59-0070, 59-0072, 59-0099, 59-0102, the benzothiazole counterpart of 59-0104, 59-0144, 59-0147, 59-0149, 59-0186, 59-0187, 59-0192, 59-0193, 59-0195, 59-0197, 59-0202, 59-0204, 59-0205, 59-0206, 59-0207, 59-0208, and 59-0210, especially the benzothiazole counterpart of 59-0104 or compounds 59-0147, 59-0205 or 59-0210. (See Figure 13)

Z can also be CR, CR_2 or O; here it is also preferred that Ar^2 is



(v)

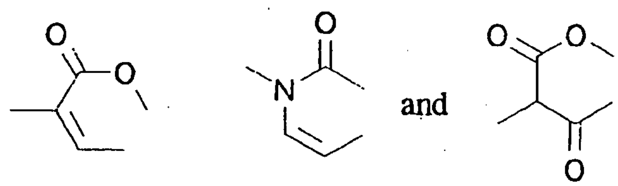
,

wherein R^b is a noninterfering substituent and n is an integer of 0-5, and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, $-CR_2NR-$, $-CR_2CR_2-$, -NRCO- or -CONR- where R is H or alkyl (1-6C), and/or the dotted line represents a π bond.

In these compounds, too, it is preferred that each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system. A preferred compound is 896-5005. (See Figure 4)

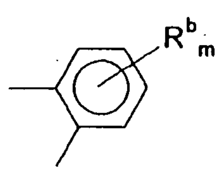
The compounds wherein Ar^1 is 1a or 2a as above may also contain a constrained linker.

In these compounds, preferred Z is S or NR; and/or those wherein L is selected from the group consisting of



; and/or

Ar^2 is

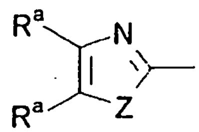


,

wherein R^b is a noninterfering substituent and m is 0-4.

Preferably, each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system. A preferred compound is 59-0124. (See Figure 13)

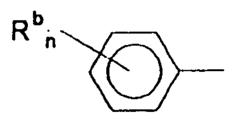
In another group of preferred embodiments, Ar^1 is of the formula



(3a)

,

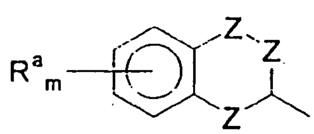
wherein each R^a is independently a noninterfering substituent or is H and Z is NR, S or O, wherein R is alkyl (1-6C) or H, especially where Z is S and/or wherein Ar^2 is



(v)

wherein R^b is a noninterfering substituent and n is an integer of 0-5,; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, $-CR_2NR-$, $-CR_2CR_2-$, -NRCO- or -CONR- where R is H or alkyl (1-6C), and/or the dotted line represents a π bond. Especially preferred are those compounds where each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

In another group of compounds, Ar^1 is

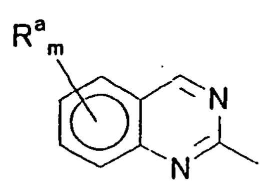


(4a)

,

wherein R^a is a noninterfering substituent, m is an integer of 0-4, each dotted line represents an optional π-bond, each Z is independently N, NR, CR or CR_2, where each R is independently H or alkyl (1-6C) with the proviso that at least one Z is N or NR.

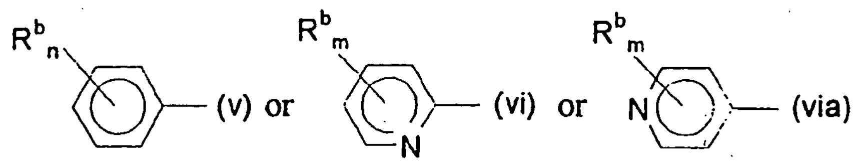
Particularly preferred members of this group are those wherein Ar^1 is



(5a)

,

especially those wherein Ar_2 is

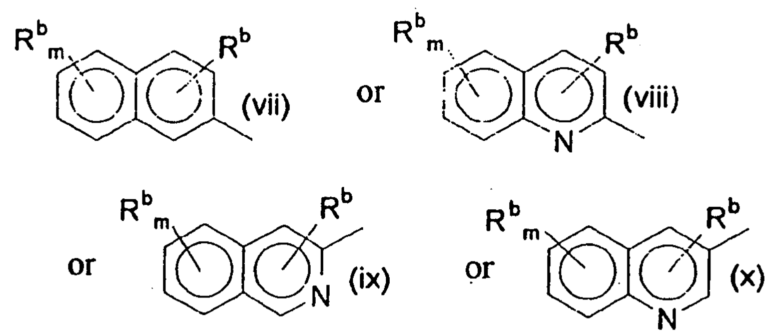


wherein each R^b is independently a noninterfering substituent, and n is 0-5 and m is 0-4, and/or L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, $-NRCR_2-$, $-NRCR_2CR_2-$, $-NRCR_2CO-$, -NRNR-, $-CR_2CR_2-$, $-NRCR_2CR_2NR-$, -NRCR=CRNR- or $-NRCOCR_2NR-$.

In general, preferably each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

In an especially preferred group, m is 0, each R^b is NR_2 or OR and n is 1 or 2, and/or L is -CR=CR-, -N=N- or -NRCO-, especially the compounds of formulas 59-0030, 59-0078, 59-0091, 59-0093, 59-0150, 50-0197, 59-0198, 59-0199 or 59-0480. (See Figure 13)

Also preferred are those wherein Ar^1 has formula (4a) or (5a) and wherein Ar_2 is substituted or unsubstituted quinolyl or naphthyl of the formula

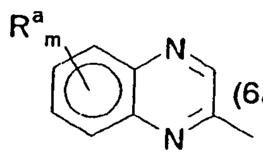
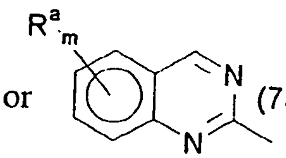
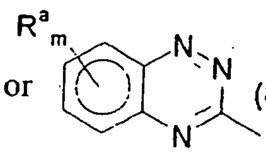


wherein each R^b is a noninterfering substituent and m is 0-4.

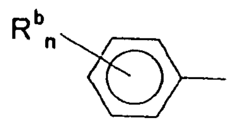
Preferred among these are those wherein L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, $-NRCR_2-$, $-NRCR_2CR_2-$, $-NRCR_2CO-$, -NRNR-, $-CR_2CR_2-$, $-NRCR_2CR_2NR-$, -NRCR=CRNR- or $-NRCOCR_2NR-$, and/or wherein each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system and m is 0, 1 or 2.

The compounds 59-0089, 59-0090, 59-0092 or 59-0094 are particularly preferred.

Ar^1 is also preferably


(6a) or

(7a) or

(8a)

wherein each R^a is a noninterfering substituent and m is 0-4, in particular where L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, $-NRCR_2-$, $-NRCR_2CR_2-$, $-NRCR_2CO-$, -NRNR-, $-CR_2CR_2-$, $-NRCR_2CR_2NR-$, -NRCR=CRNR- or $-NRCOCR_2NR-$, and/or Ar^2 is

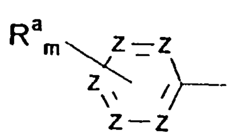

(v)

,

wherein R^b is a noninterfering substituent and n is an integer of 0-5. Especially preferred are compounds wherein each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system, in particular compounds 59-203, 59-285 or 59-286. (See Figure 13)

When Ar^1 is of formula (4a), L can also be a constrained linker.

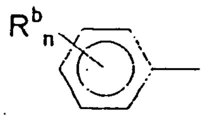
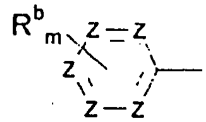
In still another preferred set, Ar^1 is


(9a)

,

wherein each R^a is independently a noninterfering substituent, m is an integer of 0-4, each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be N and at least one Z must be CR.

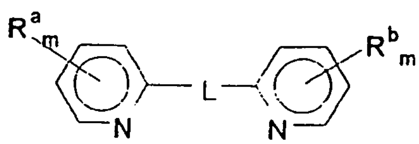
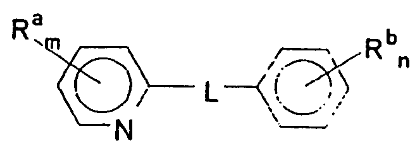
In these compounds, L is preferably a flexible conjugating or nonconjugating linker, and/or wherein Ar^2 is

 (v) or  (vi)

,

wherein each R^b is independently a noninterfering substituent, and in (vi) each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be a N and at least one Z must be CR.

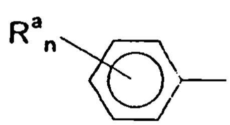
Preferred such compounds have the formula

 or 

Preferred L embodiments in this group include -N=N-, -RC=CR-, -RC=N-, -NRCO-, $-NRCR_2-$, $-NRCR_2CR_2-$, $-NRCR_2CO-$, -NRNR-, $-CR_2CR_2-$, $-NRCR_2CR_2NR-$, -NRCR=CRNR- or $-NRCOCR_2NR-$; preferred for R^a and R^b are halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^a or R^b comprise aromatic systems and each m and n is independently 0, 1 or 2.

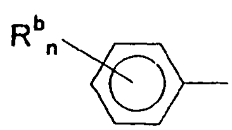
In particular, compounds are preferred where L is $-NHCR_2CR_2NH-$ and R^a is CF_3 para to L, especially compounds 59-0145, 59-0450, 59-0459 or 59-0483. (See Figure 13)

Finally, in another preferred group, Ar^1 is

 (10a)

,

wherein each R^a is a noninterfering substituent, and n is an integer of 0 and 5, and wherein L is a flexible linker that contains at least one nitrogen. In the alternative or in addition, Ar^2 is of the formula

 (v)

and L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, $-NRCR_2-$, $-NRCR_2CR_2-$, $-NRCR_2CO-$, $-NRNRCR_2CR_2-$, -NRNRCR=CR-, $-NRNRCOCR_2-$, -NRNRCOCR=CR-, $-NRNRCSCR_2-$, -NRNRCSCR=CR-, -NRNRCONR-, -NRNRCSNR-, -NRNR-, $-CR_2CR_2-$, $-NRCR_2CR_2NR-$, -NRCR=CRNR- or $-NRCOCR_2NR-$. It is preferred that each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

Especially preferred are those compounds wherein L is -CR=CRCONRNR-, -CR=CRCSNRNR-, $-CR_2CONRNR-$ $-CR_2CSNRNR-$, -NRNRCONR- or -NRNRCSNR- and/or R^b is $-NR_2$ and n=1 wherein R^b is in the para position, especially wherein R^a is -COOR and m is 1; most especially compounds 59-0045, 59-0095, 59-0096, 59-0097 and 59-0098. (See Figure 13)

As set forth above, several families of preferred embodiments are defined by specifying Ar^1 and Ar^2, and L. In one such family, wherein Ar^1 is an aromatic system containing a 5-membered heterocyclic ring, the compound 59-0072, wherein Ar^1 is unsubstituted benzothiazole, the linker ($Ar^1 \rightarrow Ar^2$) is NHCO, and Ar^2 is 2-methoxy-4-methylthiophenyl was used as a lead compound and variations of the structure studied. Figure 5 shows representative compounds synthesized to analyze the effects of the nature of the linker, various alternatives of Ar^1 wherein Z is O, NR or S, and the effect of substitution on the phenyl moiety, as well as the heterocycle.

Figure 5 gives the structures of these compounds, along with their maximum activity as compared to 59-0008 at 10 μM (the maximum for 59-0008) in the *in vitro* bone growth stimulation assay as well as the concentration at which 50% of maximum stimulation of the BMP promoter was obtained (EC_{50}). See Example 1 for the details of this assay. The results of this study indicate that the amide linker in 59-0072 can readily be substituted by -CH=CH- and that the substitution on the phenyl ring had advantageous effects in the order: 2-Cl-4-OMe=2,4-di-OMe=2-OMe-4-SMe >>3,4-di-OMe=4-OMe. In general, compounds 59-0205, 59-0104, 59-0107, 59-0210 and 59-0124 have the best activity in the primary screen, but only 59-0124 is active in the *ex vivo* calvarial assay described in Example 3.

Similar structure/activity relationship studies were conducted for compounds wherein Ar^1 is quinoline. In this study, compound 50-0197, wherein Ar^1 is unsubstituted quinoline, the linker is -CH=CH-, and Ar^2 is p-dimethylaminophenyl was used as a lead compound. The compounds synthesized in this study are shown in Figure 6, along with their maximum stimulation characteristics and EC_{50} in the assay of Example 1. The results of these studies showed that quinoxaline analogs are the most active in the assay, followed by quinoline; the linker can most preferably be -CH=CH- or -N=N- as judged by activity in the assay, but -CH=CH- is preferred *in vivo* due to its lack of toxicity. Preferred substituents on the phenyl ring in Ar^2 include 2,4-di-OMe; 4-NMe_2-2-OMe, and 4-NMe_2. For the compounds in Figure 6, 59-0282 and 50-0197 were moderately active and 59-0203 was highly active in the *ex vivo* calvarial assay described hereinabove as a modification of Gowen, M. and Mundy, G. *J Immunol* (1986) 136:2478-2482.

Another group of compounds wherein Ar^1 and Ar^2 are pyridyl heterocycles was also studied. In this case, compound 59-0145 was used as the lead compound; the linker, the nature of the substituents R^a and R^b were varied. In one instance, a quinolyl residue was substituted for a pyrimidine residue as Ar^2. Representative compounds used in this study are shown in Figure 7, along with the data from the screening assay.

Using 59-0145 as a lead, a CF_3 group in one of Ar^1 and Ar^2 appeared essential; however, one of R^a or R^b could also be NO_2 or CN. The most preferred linker is -$NHCH_2CH_2NH$-; substitution on the amino groups in L by an alkyl group appeared to reduce activity. Enhanced chain lengths also led to loss of activity.

Preferred compounds in this group, which perform better than 59-0008 in the screening assay, included 59-0450, 59-0459, 59-0480, and 59-0483.

Finally, a series in which Ar^1 is 3-carboxyphenyl was studied using 59-0045 as the lead compound. In 59-0045, L is -NHN=CH- and Ar^2 is p-dimethylaminophenyl. Figure 8 shows the compounds synthesized in this series. Under the circumstances of this assay, analogs wherein R^b was, instead of a nitrogen-containing moiety, F, Cl, or OMe were inactive. Preferred compounds in this series are 59-0096 and 59-0098. 59-0098 is very active in the *ex vivo* calvarial assay described above.

Synthesis of the Compounds Useful in the Invention

Many of the compounds useful in the invention are commercially available and can be synthesized by art-known methods. Those compounds useful in the invention which are new compounds, can similarly be obtained by methods generally known in the art, as described in the Examples below.

The following examples are intended to illustrate, but not to limit, the invention.

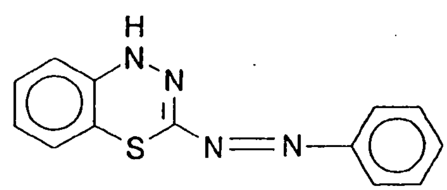
Preparation A

Compound 59-0008 used as a standard in the assays, was synthesized according to the procedure of McDonald, W. S., *et al. Chem Comm* (1969) 392-393; Irving, H. N. N. H. *et al. Anal Chim Acta* (1970) 49:261-266. Briefly, 10.0 g of dithizone was taken up in 100 ml EtOH and 50 ml AcOH and heated at reflux for 18 h. After cooling, this was diluted first with 100 ml water and then with 50 ml 1N NaOH. This was then further neutralized by the addition of 6 N NaOH to bring the pH to 5.0. This deep purple mixture was then concentrated on a rotavapor to remove organics. Once the liquid had lost all of its purple color, this was filtered to collect the dark precipitate. Purification by flash chromatography (4.5 x 25.7 cm; EtAc/Hep. (1:4); R_f 0.22) followed by recrystalization from EtOH gave 2.15 g (25% yield) of dark purple crystals, mp=184-185 ^oC. ^1H NMR ($CDCl_3$) 7.90 (d of d, J_1=7.7, J_2=2.2, 2H), 7.64 (hump, 1H), 7.49 (m, 3H), 7.02 (m, 1H), 6.91 (m, 2H), 6.55 (d, J=8.1, 1H). MS (EI) 254 (47, M+), 105 (26), 77 [100], 51 (27). HRMS (EI, M+) 254.0626 (calcd 254.0626182). Anal. Calcd for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.03. Found: C, 61.40; H, 4.20; N, 22.06.

Example 1

High Throughput Screening

Several tens of thousands of compounds were tested in the assay system set forth in WO 96/38590, published 5 December 1996, and incorporated herein by reference. The standard positive control was 59-0008 (also denoted "OS8"), which is of the formula:



"OS8"

In more detail, the 2T3-BMP-2-LUC cells, a stably transformed osteoblast cell line described in Ghosh-Choudhury *et al. Endocrinology* (1996) 137:331-39, referenced above, was employed. The cells were cultured using α-MEM, 10% FCS with 1% penicillin/streptomycin and 1% glutamine ("plating medium"), and were split 1:5 once per week. For the assay, the cells were resuspended in a plating medium containing 4% FCS, plated in microtiter plates at a concentration of 5×10^3 cells (in 50 μl)/well, and incubated for 24 hours at 37°C in 5% CO_2. To initiate the assay, 50 μl of the test compound or the control in DMSO was added at 2X concentration to each well, so that the final volume was 100 μl. The final serum concentration was 2% FCS, and the final DMSO concentration was 1%. Compound 59-0008 (10 μM) was used as a positive control.

The treated cells were incubated for 24 hours at 37°C and 5% CO_2. The medium was then removed, and the cells were rinsed three times with PBS. After removal of excess PBS, 25 μl of 1X cell culture lysing reagent (Promega #E153A) was added to each well and incubated for at least ten minutes. Optionally, the plates/samples could be frozen at this point. To each well was added 50 μl of luciferase substrate (Promega #E152A; 10 ml Promega luciferase assay buffer per 7 mg Promega luciferase assay substrate). Luminescence was measured on an

automated 96-well luminometer, and was expressed as either picograms of luciferase activity per well or as picograms of luciferase activity per microgram of protein.

In this assay, compound 59-0008 (3-phenylazo-1H-4,1,2-benzothiadiazine) exhibited a pattern of reactivity, as shown in Figure 2. The activity for compound 59-0008 was maximal at a concentration of approximately 3-10 μM and, more particularly, at about 3 μM, and thus provided a response of approximately 175 light emission units. Accordingly, other tested compounds were evaluated at various concentrations, and these results were compared to the results obtained for 59-0008 at 10 μM (which value was normalized to 100). For instance, any tested compound in Figure 3 and Figure 4 that showed greater activity than 10 μM of 59-0008 would result in a value over 100.

As shown in Figure 3 (46 sheets) and Figure 4 (28 sheets), several compounds were found to be particularly effective.

Example 2

In vivo Calvarial Bone Growth Data

Compound 59-0008 was assayed *in vivo* according to the procedure described previously (see "*In vivo* Assay of Effects of Compounds on Murine Calvarial Bone Growth", *supra*). As compared to a vehicle control, compound 59-0008 induced a 4-fold increase in width of new calvarial bone.

In another experiment, 5 week old Swiss white mice were injected 3 times a day for 5 days over the calvaria with compound 59-0203 using PBS, 5% DMSO and 0.1% BSA as carrier. The drug was tested at 6 different doses, from 0.1-50 mg/kg/day. Animals were sacrificed 3 weeks after the injections started and calvariae were fixed, decalcified, and processed for histology. Bone histomorphometry measuring total bone area (BA/TV) confirms that FGF, used in every experiment as a positive control, shows an increase in the total bone area with all doses tested, but this increase is only significantly different from control at 1 and 5 mg/kg/day. The invention compound 59-0203 shows consistent increases over the 0.1-50 mg/kg/day range at a somewhat lower level than that obtained with FGF.

Similar results are obtained when new bone width in microns is measured. There was no new bone present in the control group. 59-0203 caused new bone formation at all doses, with a significant increase at 25-50 mg/kg/day. New bone as percentage of the total bone area was about 45% for the FGF positive control and from about 15% to 30% over the range of 0.1-50 mg/kg/day for 59-0203. There was no new bone present in the negative control.

Example 3

Ex vivo Calvarial Bone Growth Assay

A number of compounds, in particular, those studied in connection with lead compounds classified as hydrazone/hydrazides (H) exemplified by 59-0045, benzothiazoles (T) exemplified by 59-0104, bis-pyridines (P) exemplified by 59-0145, and quinolines/quinoxalines (Q) exemplified by 59-0197, were tested in the *ex vivo* calvarial assay described hereinabove. The results of this assay are shown in Figure 9. In this assay, histomorphotometry and osteoblast numbers are measured and effects are measured on an arbitrary scale from 1-3: i.e., 1, 1+, 2-, 2, 2+, 3-, 3, wherein 1 denotes "inactive." In this assay, for example, FGF scores 2-3.

The scores are assigned to bone formation on the ectocranial periosteal surface. The area immediately surrounding midline suture is excluded from analysis.

Score

0 Toxicity. Cell necrosis, pyknotic nuclei, matrix disintegration.

1 A score of "1" is the bone forming activity seen in control cultures containing BGJb media + 0.1% bovine serum albumin. The periosteal surface is covered by one layer of osteoblasts (at about 50% of the bone surface, with the remaining 50% being covered by bone lining cells). A score of "1-" is assigned if less than 50% of the periosteal surface is covered by osteoblasts due to inhibitory activity or minor toxicity of the agents being tested. A score of "1+" is given if over 50% of the surface is covered by osteoblasts.

2 A moderate increase in bone forming activity. 20-40% of the periosteal surface is covered by up to two layers of osteoblasts. A score of "2-" is given if less than 20% of the surface is covered by

two layers and "2+" if more than 40% of the surface is covered by two layers of osteoblasts.

3 A score of "3" is the bone forming activity seen in control cultures containing BGJb media + 0.1% BSA +10% fetal bovine serum. More than 20% of the periosteal surface is covered by three layers of osteoblasts. The cells appear plump (size can exceed 100μm2). A score of "3-" is given if less than 20% of the periosteal surface is covered by three layers of osteoblasts and or osteoblast size is less than 100μm2. A score of "3+" has never been observed.

In all samples, toxicity, ectopic new or woven bone formation associated with osteoblasts, and osteoblast size as reflections of relative activity are noted.

The results shown in Figure 9 represent those obtained when the measurements were made by two different groups. It is clear that a number of compounds tested have activity in this assay. From the results shown in Figure 9, 59-0073, 59-0030, 59-0070, 59-007, 59-0019, 59-0099, 59-0072 and 59-0103 show at least some indication of activity. 59-150 and 59-0104 showed activity when measured by one group but not the other; similarly, 50-0197 had this pattern. It appears that 59-0098 and 59-0203 are quite active in this assay and 59-0145 shows a consistent moderate activity.

Example 4

Stimulation of Bone Growth in Ovariectomized Rats (OVX Assay)

The compound 59-0145 was tested at various concentrations in the OVX assay conducted as described above. The increase in bone volume was measured by two different groups; one group found 5 μg/kg/day of 59-0145 gave 21% increase over control whereas the second group found a 71% increase. At 50 μg/kg/day, the first group found a 31% increase, and the second a 54% increase.

In another experiment, the lumbar vertebrae were measured and the above dosages of 59-0145 were shown to provide a beneficial effect, as shown in Figure 10.

In another experiment, 3 month old Sprague Dawley rats were ovariectomized and depleted for six weeks. At the end of the six weeks, treatment was started with subcutaneous administration of compound 59-0145. The treatment continued for 10

weeks. At the end of the 10 weeks animals were sacrificed, bones were collected for qCT measurements and histology; serum was also collected for osteocalcin determinations.

Figure 11 shows the percentage increase in trabecular bone (proximal tibia) compared to the placebo-treated group in chronic ovariectomized rats after 10 weeks of treatment. Compound 59-0145 causes significant increase in trabecular bone at doses of 50-500 μg/kg/day.

Figure 12 shows results of qCT and bone histomorphometry in proximal tibia in the first two panels, as well as serum osteocalcin levels at the time of sacrifice as a percentage increase compared to control group (OVX placebo-treated group).

Example 5

Chondrogenic Activity

Compounds 59-008, 59-0102 and 50-0197 were assayed for effects on the differentiation of cartilage cells, as compared to the action of recombinant human BMP-2. Briefly, a mouse clonal chondrogenic cell line, TMC-23, was isolated and cloned from costal cartilage of transgenic mice containing the BMP-2 gene control region driving SV-40 large T-antigen, generated as described in Ghosh-Choudhury *et al Endocrinology* 137:331-39, 1996. These cells were cultured in DMEM/10% FCS, and were shown to express T-antigen, and also to produce aggrecan (toluidine blue staining at pH 1.0) and Type-II collagen (immunostaining) by 7 days after confluence.

For measurement of alkaline phosphatase (ALP) activity, the technique of LF Bonewald *et al. J Biol Chem* (1992) 267:8943-49, was employed. Briefly, TMC-23 cells were plated in 96 well microtiter plates in DMEM containing 10% FCS at 4 x 10^3 cells/well. Two days after plating, the cells were confluent and the medium was replaced with fresh medium containing 10% FCS and different concentrations of compounds or recombinant BMP-2. After an additional 2 or 5 days incubation, the plates were washed twice with PBS, and then lysing solution (0.05% Triton X-100) was added (100 μl/well). The cells were lysed by three freeze-thaw cycles of -70°C (30 min), followed by 37°C (30 min with shaking). Twenty microliters of cell lysates

were assayed with 80 µl of 5 mM p-nitrophenol phosphate in 1.5 M 2-amino-2-methyl-propanol buffer, pH 10.3 (Sigma ALP kit, Sigma Chemical Co., St. Louis, MO) for 10 min at 37°C. The reaction was stopped by the addition of 100 µl of 0.5 M NaOH. The spectrophotometric absorbance at 405 nm was compared to that of p-nitrophenol standards to estimate ALP activity in the samples. The protein content of the cell lysates was determined by the Bio-Rad protein assay kit (Bio-Rad, Hercules, CA). Specific activity was calculated using these two parameters.

At day 2, compounds 59-0008 (10^{-9} M), 59-0102 (10^{-7} M) and 59-0197 (10^{-9} M) increased ALP levels approximately 3-, 2- and 2.5-fold, respectively, as compared to the vehicle control. Recombinant BMP2 at 100, 50 or 10 ng/ml induced ALP levels approximately 10-, 4- or 1.5-fold, respectively, as compared to the vehicle control.

Example 6

Synthesis of Exemplary Compounds

A. Compounds of the invention wherein Ar^1 is of formula (1a) or (2a) can be synthesized by the procedures described in Dryanska, V. and Ivanov, K. *Synthesis* (1976) 1:37-8, using the described embodiments of Ar^2 and the appropriate analogous heterocycle embodied in Ar^1 substituted for the benzothiazole shown. Alternates to the olefin linker described can also be prepared using standard methods.

Compounds of the invention represented by exemplary Compound 59-0234, wherein Z is O, L is -CH=CH-, and Ar^2 is 2,4-dimethyoxy-phenyl, including Compounds 59-0211 and 59-0233, were prepared according to the following procedure describing synthesis of Compound 59-0234. Briefly, to a N,N-dimethylformamide (DMF) solution of 2-methylbenzoxazole (1 mmol) and 2,4-dimethoxybenzaldehyde (1 mmol) was added lithium t-butoxide (2 mmol). The reaction mixture was heated at 130°C for 3h. After cooling to room temperature, the reaction mix was poured into ether and washed several times with water. The organic phase was dried over Na_2SO_4, filtered. and evaporated to dryness. The residue was dissolved in a minimal amount of hot ether and, on standing overnight, the crystalline product was collected by filtration.

B. Exemplary Compound 59-0150 where Ar^1 is of formula 4a was synthesized according to the procedure of Zamboni *et al. J Med Chem* (1992) 35:3832-44. First, 2-triphenylphosphoniumquinaldine bromide was synthesized as follows. Quinaldine (200 mmols), NBS (200 mmols) and a catalytic amount of benzoyl peroxide (10 mmols) were dissolved in 1 L of anhydrous carbon tetrachloride, and the mixture was stirred under reflux for 72 h. The mixture was cooled to RT and washed with water. The organic layer was drawn off, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to a dark oil. The crude mixture was dissolved in 500 ml of acetonitrile, then triphenylphosphine (200 mmols) was added and the mixture was refluxed under nitrogen overnight. It was then cooled to RT and diluted with anhydrous ether. The precipitated solid was collected by filtration, washed thoroughly with anhydrous ether and dried in vacuo overnight, yielding 25 g of a tan crystalline solid which showed a single spot by TLC (silica gel, 5 % MeOH in DCM).

A Wittig reaction was then performed. Briefly, under anhydrous conditions, 0.738 g (1.68 mmol) 2-triphenylphosphoniumquinaldine bromide in dry THF was cooled to -78°C. 1.0 ml (2.5 mmol, 2.5 M in hexanes) n-butyl lithium was slowly added, and this was allowed to react for 20 min. 0.301 g (1.68 mmol) 4-(N,N-dimethylamino)-2-methoxybenzaldehyde was then added. After a few minutes, the cold bath was removed, and this was left at ambient temp. for 18 h. The reaction was quenched by the addition of aq. sat. NH_4Cl. This was extracted with EtAc, and the organics washed with additional NH_4Cl, sat. $NaHCO_3$, and sat. NaCl. This was dried over anhydrous Na_2SO_4 and the solvent stripped on a rotavapor. After flash chromatography (3.8 x 18.0 cm; EtAc/Hep. (1:3); R_f 0.29), 0.135 g (26% yield) of a red solid was obtained, mp=185-187 ^oC. ^1H NMR ($CDCl_3$) 8.04 (t, J=9.0, 2H), 7.94 (d, J=16.5, 1H), 7.74 (d, J=8.1, 1H), 7.73 (d, J=8.5, 1H), 7.66 (t of d, J_t=7.6, J_d=1.4, 1H), 7.61 (d, J=8.8, 1H), 7.43 (t of d, J_t=7.6, J_d=1.1, 1H), 7.29 (d, J=16.6, 1H), 6.37 (d of d, J_1=8.7, J_2=2.4, 1H), 6.22 (d, J=2.4, 1H), 3.93 (s, 3H), 3.03 (s, 6H).. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found:

C. Exemplary Compound 59-0209 was synthesized according to the procedure of McOmie, J. F. W.; and West, D. E., *Org Synth, Collect Vol V* (1973) 412. Under anhydrous conditions, 0.510 g (1.95 mmol) NNC 59-0198 was slowly treated with 0.38 ml (3.9 mmol) BBr_3 in dry CH_2Cl_2 at -78°C. After 15 min, this was allowed to warm to RT. After 2 h, the reaction was re-cooled to -78°C, and was then quenched by the addition of 1.6 ml (12 mmol) TEA in 25 ml MeOH. After 10 min, this was again allowed to warm to ambient temperature. After 1 h, this was concentrated to dryness on a rotavapor, and twice slurred in MeOH and re-stripped. Purification by flash chromatography (3.0 x 25.6 cm; EtAc/Hep. (1:2); R_f 0.25) gave 0.20 g (41% yield) of a slightly yellow solid, mp=271-272 °C (dec.). ^1H NMR (DMSO-d6) 9.77 (s, 1H), 8.31 (d, J=8.6, 1H), 7.96 (d, J=8.6, 1H), 7.92 (d, J=8.3, 1H), 7.82 (d, J=8.6, 1H), 7.74 (d, J=16.6, 1H), 7.72 (t, J=7.6, 1H), 7.58 (d, J=8.6, 2H), 7.53 (t, J=7.6, 1H), 7.26 (d, J=16.5, 1H), 6.83 (d, J=8.6, 2H). Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found:

D. Exemplary Compound 59-0019 was synthesized as follows: to a xylene solution of 2-methylquinoxaline (10 mmol) and 4-dimethylaminobenzaldehyde (10 mmol) was added piperdine (2 ml). The solution was heated at reflux for 1 day, at which time DBU (200 μL) was added and reflux continued for another 2 days. The solution was cooled to RT and extracted with 1 M citric acid. The aqueous phase was repeatedly extracted with ether. The organic phases were pooled, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was chromatographed on silica gel. The product was eluted using 8:1:1 dicholormethane:ether: hexane. Fractions containing pure product were pooled and evaporated to dryness. The residue was triturated with ether and filtered to give the desired compound.

E. Exemplary Compound 59-0183 and related Compound 59-0182 were synthesized according to the following procedure. Briefly, quinaldic acid (0.5 mmol) and HATU (0.5 mmol) were dissolved in 2.5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (1 mmol) was added dropwise to the above stirred solution and the mixture was stirred for 15 min. The appropriate amine (0.5 mmol) was then added all at once to the above stirred

mixture, and the mixture was stirred overnight at RT. It was then diluted with 25 mL of cold water with vigorous stirring, the precipitate was collected by filtration and washed thoroughly with water several times, and then dried *in vacuo* overnight. The product was purified by flash column chromatography over silica gel eluting with dichloromethane. The pure product was obtained as a tan powder.

F. Exemplary Compound 59-0209 was synthesized according to the following procedure. Under anhydrous conditions, 0.510 g (1.95 mmol) NNC 59-0198 was slowly treated with 0.38 ml (3.9 mmol) BBr_3 in dry CH_2Cl_2 at -78°C. After 15 min, this was allowed to warm to RT. After 2 h, the reaction was re-cooled to -78°C, and was then quenched by the addition of 1.6 ml (12 mmol) TEA in 25 ml MeOH. After 10 min, this was again allowed to warm to ambient temperature. After 1 h, this was concentrated to dryness on a rotavapor, and twice slurred in MeOH and re-stripped. Purification by flash chromatography (3.0 x 25.6 cm; EtAc/Hep. (1:2); R_f 0.25) gave 0.20 g (41% yield) of a slightly yellow solid, mp=271-272 °C (dec.). ^1H NMR (DMSO-d6) 9.77 (s, 1H), 8.31 (d, J=8.6, 1H), 7.96 (d, J=8.6, 1H), 7.92 (d, J=8.3, 1H), 7.82 (d, J=8.6, 1H), 7.74 (d, J=16.6, 1H), 7.72 (t, J=7.6, 1H), 7.58 (d, J=8.6, 2H), 7.53 (t, J=7.6, 1H), 7.26 (d, J=16.5, 1H), 6.83 (d, J=8.6, 2H). Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found:

G. Other embodiments wherein AR^1 is of formula (4a) can be synthesized as follows:

a. Quinoline azo compounds (59-0030 and 59-0078) may be prepared by reaction of 2-aminoquinoline with a nitrosobenzene (Brown, E. V., *et al*, *J Org Chem* (1961) 26:2831-33; Brown, E. V; ____________ (1969) 6:571-73).

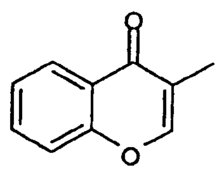
b. Azo derivatives may be obtained by reaction of 2-aminoquinolines with aldehydes, Morimoto, T., *et al.*, *Chem Pharm Bull* (1977) 25:1607-09; Renault, J., *et al.*, *Hebd Seances Acad Sci, Ser C* (1975) 280:1041-43; and Lugovkin, B. P.; *Zh Obshch Khim* (1972) 42:966-69.

c. Imino derivatives may be obtained by reaction of 2-formylquinolines with anilines, Tran Quoc Son, *et al.*, (1983) 21:22-26; Hagen,

V. *et al. Pharmazie* (1983) 38:437-39; and Gershuns, A. L., *et al., Tr Kom Anal Khim, Akad Nauk SSSR* (1969) 17:242-50.

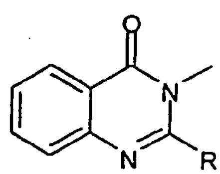
d. Alternatively conjugated linkers can be formed by bromination of the olefin of 50-0197 with Br_2 in AcOH followed by elimination with DBU as set forth in Zamboni *et al. J Med Chem* (1992) 35:3832-44.

H. Analogs having the constrained linker depicted below:



may be synthesized by reference to the methods described in Gorbulenko, N.V. *et al. Dokl Akad Nauk Ukr SSR* (1991) 5:117-23, substituting the 6-membered heterocycle for benzothiazole.

Related, compounds having the constrained linker depicted below:



R= alkyl, OH

may be synthesized by reference to the methods described in the following publications: Chaurasia, M.R. & Sharma, A.J. *Acta Cienc Indica Chem* (1992) 18:419-22; Kandeel, Maymona M., in *Phosphorus, Sulfur, Silicon, Relat Elem* (1990) 48:149-55; Salem, M.A. & Soliman, E.A. *Egypt J Chem* (1985) 27:779-87;Garin, J. *et al. Synthesis* (1984) 6:520-22, and Ayyangar N. R. *et al. Dyes and Pigments* (1990) 13:301-10.

I. Exemplary Compound 59-0145 can be synthesized according to the following method. Briefly, a mixture of 2-chloro-5-trifluoromethylpyridine (15 mmol), ethylenediamine (6 mmol), and diisopropylethylamine (18 mmol) was heated at reflux for 18 h. After cooling to room temperature, the solid mass was triturated with

dichloromethane. The product was filtered and then suspended in hot EtOAc:$CHCl_3$ (50:50, 800 mL) and filtered to remove insoluble material. The volume was reduced to ~200 mL by heating on a steam bath. On standing, crystals of pure product were deposited.

Related compounds may be synthesized by reference to the method described for Compound 59-0145, and by reference to the methods described in the following publications: Tzikas, A.& Carisch, C., US Patent No. 5,393,306, issued February 28, 1995; Herzig, P.& Andreoli, A., EP 580554, published January 26, 1994; Pohlke, R. & Fischer, W., DE 3938561, published May 23, 1991. Analogs containing the structure O-$(CH_2)_n$-O may be synthesized by reference to the previous citations, as well as the following publications: Kawato, T. & Newkome,G. *Heterocycles* (1990) 31:1097-104; Kameko, C. & Momose, Y. *Synthesis* (1982) 6:465-66; Tomlin, C.D.S. *et al.*, GB 1161492, published August 13, 1969.

J. Exemplary Compound 59-0097 and exemplary Compound 59-0201 were synthesized according to the following general procedure. Briefly, the isothiocyanate or isocyanate (1 mmol) was dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (2 mmol) was added dropwise to the above stirred solution followed by 3-hydrazinobenzoic acid (1 mmol), and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring. The precipitate was collected by filtration, washed thoroughly with water several times, and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 % methanol in dichloromethane. The pure product was obtained as a red to purple powder. The compounds of the invention are produced by substituting for at least one phenyl group the appropriate heterocycle.

K. Compounds of the class represented by exemplary Compound 59-0045 can be synthesized using standard procedures for the synthesis of phenyl hydrazones of aromatic aldehydes, as described in any organic textbook. The synthesis of exemplary Compound 59-0045 may be performed as follows. Briefly, a suspension of 3-hydrazinobenzoic acid (1 mmol), p-dimethylaminobenzaldehyde (1 mmol), and AcOH

(50 μL) in EtOH:H_2O (4 mL:1 mL) was heated at 105°C in a sealed vial for 3 h. After cooling, a bright yellow solid was removed by filtration. The solid was washed with cold MeOH and then with ether to give pure product.

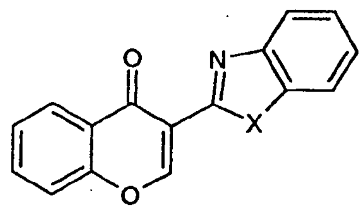
L. Exemplary Compound 59-0096 and related, exemplary Compounds 59-0098, 59-0095, 59-0107, 59-0108, 59-0109, 59-0110 and 59-0200 may be synthesized according to the following general procedure. Briefly, the appropriate carboxylic acid (1 mmol) and HATU ([O-(7-azabenzotriazol-1-yl)-1,1,3,3-tritetramethyluronium hexafluorophosphate]; 1 mmol) were dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (3 mmol) was added dropwise to the above stirred solution and the mixture was stirred for 15 min. 3-Hydrazinobenzoic acid (1 mmol) was then added all at once to the above stirred mixture and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring and the precipitate was collected by filtration and washed thoroughly with water several times and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 - 10 % methanol in dichloromethane. The pure product was obtained as a tan crystalline solid.

M. Exemplary Compound 59-0097 and exemplary Compound 59-0201 were synthesized according to the following general procedure. Briefly, the isothiocyanate or isocyanate (1 mmol) was dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (2 mmol) was added dropwise to the above stirred solution followed by 3-hydrazinobenzoic acid (1 mmol), and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring. The precipitate was collected by filtration, washed thoroughly with water several times, and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 % methanol in dichloromethane. The pure product was obtained as a red to purple powder.

N. Exemplary Compound 59-0125 where R^1 is methoxy, m is 1, the linker is azo and Ar^2 is di(2-hydroxyethyl) amino, and related compounds having an azo

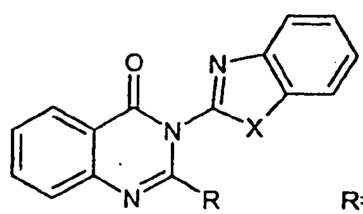
linker can be prepared in a manner similar to that described by Alberti, G. *et al. Chim Ind (Milan)* (1974) 56:495-97.

O. Exemplary Compound 59-0124 and related, constrained analogs having the structure depicted below:



may be synthesized by reference to the methods described in Gorbulenko, N.V. *et al. Dokl Akad Nauk Ukr SSR* (1991) 5:117-23.

Related, constrained analogs having the structure depicted below:



R= alkyl, OH

may be synthesized by reference to the methods described in the following publications: Chaurasia, M.R. & Sharma, A.J. *Acta Cienc Indica Chem* (1992) 18:419-22; Kandeel, Maymona M., in *Phosphorus, Sulfur, Silicon, Relat Elem* (1990) 48:149-55; Salem, M.A. & Soliman, E.A. *Egypt J Chem* (1985) 27:779-87;Garin, J. *et al. Synthesis* (1984) 6:520-22, or according to the representative procedure described in Ayyangar N. R. *et al. Dyes and Pigments* (1990) 13:301-10.

Claims

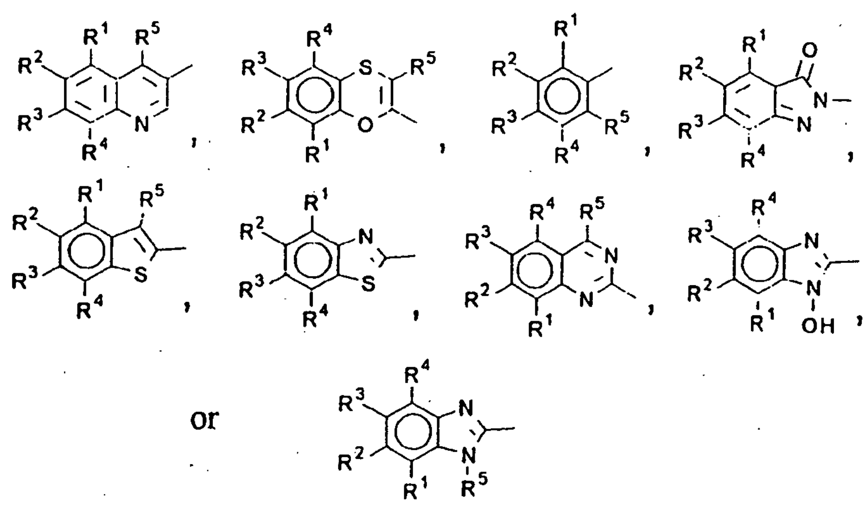
1. A method to treat a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth or replacement and/or an undesirable level of bone resorption, which method comprises administering to a vertebrate subject in need of such treatment an effective amount of a compound of the formula:

$$Ar^1\text{-}L\text{-}Ar^2$$

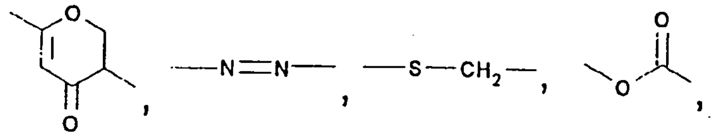
wherein each of Ar^1 and Ar^2 is independently a substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted aromatic system containing a 6-membered heterocycle or a substituted or unsubstituted aromatic system containing a 5-membered heterocycle; and

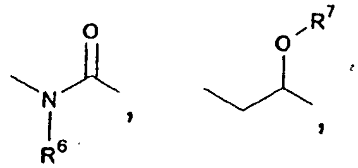
L is a linker which spaces Ar^1 from Ar^2 at a distance of 1.5Å-15Å.

2. The method of claim 1 with the proviso that in the compound of formula (1), if Ar^1 is

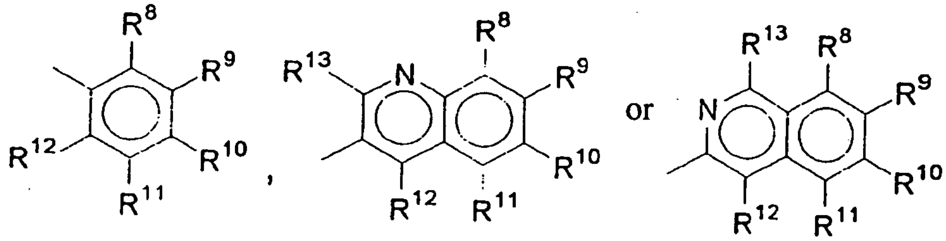


and L is



 or a single bond

Ar^2 cannot be



wherein

R^1 is selected from the group consisting of:

H, OH, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 alkylthio, halo and (C1-C12)alkyl-carbonyloxy;

R^2 is selected from the group consisting of:

H, OH, halo, C1-C6 alkyl, C1-C6 alkenyl, C1-C6 alkoxy and (C1-C12)alkyl-carbonyloxy;

R^3 is selected from the group consisting of:

H, OH, halo, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkenyl and (C1-C12)alkyl-carbonyloxy;

R^4 is selected from the group consisting of:

H, OH, halo, C1-C6 alkyl, C1-C6 alkoxy and (C1-C12)alkyl-carbonyloxy;

R^5 is selected from the group consisting of:

H, halo, C1-C6 alkyl, C1-C6 alkoxy, -OC(=O)Me, phthalimide and (C1-C12)alkyl-carbonyloxy;

R^6 is selected from the group consisting of:

H, OH, $-NH_2$, Cl-C4 alkyl and C1-C4 alkoxy;

R^7 is selected from the group consisting of:

H, C1-C4 alkyl, (C1-C4)alkyl-carbonyl and (C7-C10)arylalkyl;

R^8 is selected from the group consisting of:

H, OH, halo, $-CF_3$, C1-C4 haloalkyl, C1-C4 alkyl, C1-C4 alkoxy, -NHC(=O)Me and -N(C1-C4 alkyl)$_2$;

R^9 is selected from the group consisting of:

H, OH, halo, -CN, $-NO_2$, C1-C4 haloalkyl, C1-C8 alkyl, C1-C8 alkoxy, -NHC(=O)Me and -OC(=O)Me;

R^{10} is selected from the group consisting of:

H, OH, halo, -CN, $-NO_2$, C1-C4 haloalkyl, $-CO_2H$, C1-C12 alkyl, C1-C12 alkoxy, phenyl, C1-C12 alkenyl, (C1-C4)alkoxycarbonyl, -NHC(=O)Me, (C1-C4)alkylcarbonyl, (C1-C12)alkylcarbonyloxy and heteroaryl;

R^{11} is selected from the group consisting of:

H, OH, halo, C1-C4 haloalkyl, $-CF_3$, C1-C4 alkyl, $-NH_2$, C1-C4 alkoxy, -NHC(=O)Me, C1-C4 alkenyl, (C1-C4)alkoxycarbonyl, (C1-C4)alkylcarbonyl, and (C1-C4)alkylcarbonyloxy;

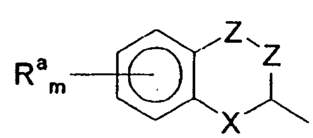
R^{12} is selected from the group consisting of:

H, OH, $-NH_2$, C1-C4 alkyl, C1-C4 alkoxy and (C1-C4)alkylcarbonyl; and

R^{13} is selected from the group consisting of:

H, OH, halo, $-NH_2$, C1-C4 alkyl, C1-C4 alkoxy -N(C1-C4)alkyl.

3. The method of claim 1 with the proviso that in the compound of formula (1), if Ar^1 is



Ar^1

;

wherein R^a is a noninterfering substituent;

m is an integer of 0-4;

each dotted line represents an optional π-bond;

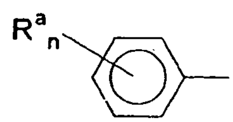
each Z is independently N, NR, O, S, CR or CR_2, where each R is independently H or alkyl (1-6C);

X is O, S, SO or SO_2; and

L is a flexible linker,

then Ar^2 is not a substituted or unsubstituted 6-membered aromatic ring;

if Ar^1 is



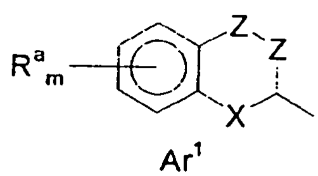
;

wherein R^a is a noninterfering substituent;

n is an integer of 0 and 5; and

L is a flexible linker which does not contain nitrogen or is a constrained linker, then Ar^2 is not a substituted or unsubstituted phenyl or a substituted or unsubstituted naphthyl.

4. The method of claim 2 with the further proviso that in the compound of formula (1), if Ar^1 is



;

wherein R^a is a noninterfering substituent;

m is an integer of 0-4;

each dotted line represents an optional π-bond;

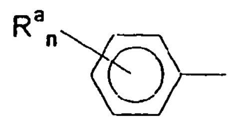
each Z is independently N, NR, O, S, CR or CR_2, where each R is independently H or alkyl (1-6C);

X is O, S, SO or SO_2; and

L is a flexible linker,

then Ar^2 is not a substituted or unsubstituted 6-membered aromatic ring;

if Ar^1 is



;

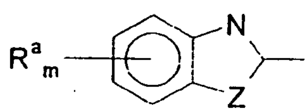
wherein R^a is a noninterfering substituent;

n is an integer of 0 and 5; and

L is a flexible linker which does not contain nitrogen or is a constrained linker,

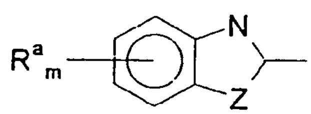
then Ar^2 is not a substituted or unsubstituted phenyl or a substituted or unsubstituted naphthyl.

5. The method of any of claims 1-4 wherein Ar^1 is



(1a)

or



(2a)

wherein each R^a is a noninterfering substituent;

m is an integer of 0-4;

the dotted line represents an optional π bond;

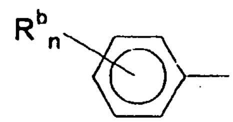
Z is O, S, NR or CR_2 in formula (1) or is CR in formula (2) where each R is independently H or alkyl (1-6C); and

L is a flexible conjugating or nonconjugating linker or is a constrained linker.

6. The method of claim 5 wherein L is a flexible conjugating or nonconjugating linker.

7. The method of claim 6 wherein Z is NR.

8. The method of claim 7 wherein Ar^2 is a substituted or unsubstituted aromatic system containing a 5-membered heterocycle or is


(v)

;

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or

L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR_2NR-, -CR_2CR_2-, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or

the dotted line represents a π bond.

9. The method of claim 7 wherein each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

10. The method of claim 7 wherein

m is 0; and/or

each R^b is independently OR, SR or halo;

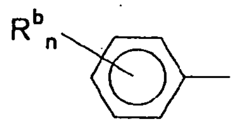
where n=2 and at least one R^b is OR or SR; and/or

L is -NHCO- or -CR=CR-.

11. The method of claim 7 wherein said compound is 59-0100, 59-103, 59-104, 59-105 or 59-106.

12. The method of claim 6 wherein Z is S.

13. The method of claim 12 wherein Ar^2 is a substituted or unsubstituted aromatic system containing a 6-membered heterocycle or is of the formula



(v)

,

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or

L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, $-CR_2NR-$, $-CR_2CR_2-$, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or

the dotted line represents a π bond.

14. The method of claim 13 wherein each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

15. The method of claim 13 wherein

m is 0; and/or

each R^b is independently OR, SR or halo;

where n=2 and at least one R^b is OR or SR; and/or

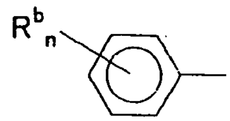
L is -NHCO- or -CR=CR-.

16. The method of claim 12 wherein the compound is compound number 59-002, 59-0070, 59-0072, 59-0099, the benzothiazole counterpart of 59-0104, 59-0102, 59-0144, 59-0147, 59-0149, 59-0186, 59-0187, 59-0192, 59-0193, 59-0195, 59-0197, 59-0202, 59-0204, 59-0205, 59-0206, 59-0207, 59-0208, and 59-0210.

17. The method of claim 16 wherein the compound is the benzothiazole counterpart of 59-0104, or is compound number 59-0147, 59-0205 or 59-0210.

18. The method of claim 6 wherein Z is CR or CR_2.

19. The method of claim 18 wherein Ar^2 is



(v)

,

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or

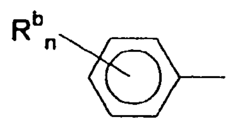
L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, $-CR_2NR-$, $-CR_2CR_2-$, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or

the dotted line represents a π bond.

20. The method of claim 19 wherein each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

21. The method of claim 6 wherein Z is O.

22. The method of claim 21 wherein Ar^2 is of the formula



(v)

,

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or

L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, $-CR_2NR-$, $-CR_2CR_2-$, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or

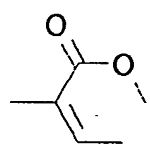
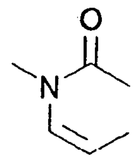
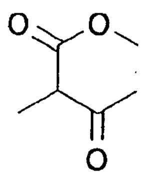
the dotted line represents a π bond.

23. The method of claim 19 wherein each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

24. The method of claim 21 wherein the compound of formula (1) is compound number 896-5005.

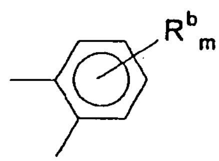
25. The method of claim 5 wherein L is a constrained linker.

26. The method of claim 25 wherein Z is S or NR; and/or wherein L is selected from the group consisting of

  and 

; and/or

wherein Ar^2 is



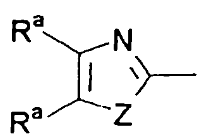
,

wherein R^b is a noninterfering substituent and m is 0-4.

27. The method of claim 25 wherein each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or comprises an aromatic system.

28. The method of claim 25 wherein the compound of formula (1) is 59-0124.

29. The method of any of claims 1-4 wherein Ar^1 is of the formula

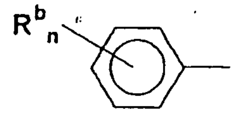


(3a)

,

wherein each R^a is independently a noninterfering substituent or is H; and Z is NR, S or O, wherein R is alkyl (1-6C) or H.

30. The method of claim 29 wherein Z is S; and/or wherein Ar^2 is



(v)

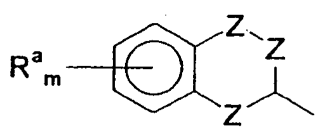
wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or

L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, $-CR_2NR-$, $-CR_2CR_2-$, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or

the dotted line represents a π bond; and/or

each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or comprises an aromatic system.

31. The method of any of claims 1-4 wherein Ar^1 is



(4a)

,

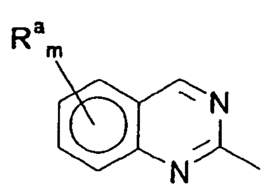
wherein R^a is a noninterfering substituent;

m is an integer of 0-4;

each dotted line represents an optional π-bond;

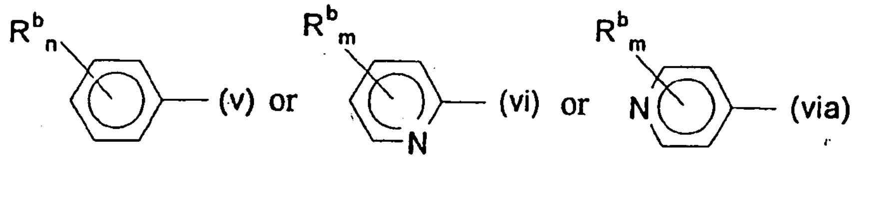
each Z is independently N, NR, CR or CR_2, where each R is independently H or alkyl (1-6C) with the proviso that at least one Z is N or NR.

32. The method of claim 31 wherein Ar^1 is



(5a)

33. The method of claim 31 wherein Ar_2 is



wherein each R^b is independently a noninterfering substituent, and n is 0-5 and m is 0-4; and/or

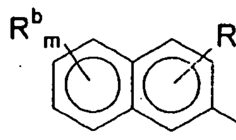
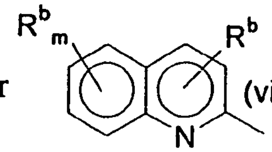
L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, $-NRCR_2-$, $-NRCR_2CR_2-$, $-NRCR_2CO-$, -NRNR-, $-CR_2CR_2-$, $-NRCR_2CR_2NR-$, -NRCR=CRNR- or $-NRCOCR_2NR-$.

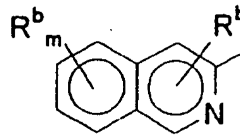
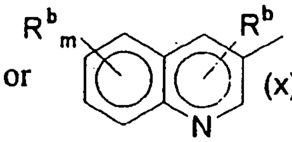
34. The method of claim 33 wherein each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

35. The method of claim 32 wherein
each R^b is NR_2 or OR and m and n are 0, 1 or 2; and/or
L is -CR=CR-,-N=N- or -NRCO-.

36. The method of claim 35 wherein the compound of formula (1) is 59-0030, 59-0078, 59-0091, 59-0093, 59-0150, 50-0197, 59-0198, 59-0199 or 59-0480.

37. The method of claim 31 wherein Ar_2 is substituted or unsubstituted quinolyl or naphthyl of the formula

 (vii) or  (viii)

or  (ix) or  (x)

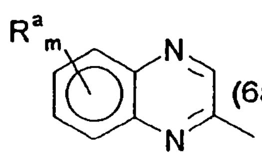
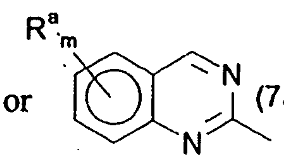
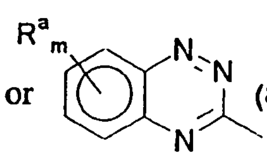
wherein each R^b is a noninterfering substituent and m is 0-4.

38. The method of claim 37 wherein L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, $-NRCR_2-$, $-NRCR_2CR_2-$, $-NRCR_2CO-$, -NRNR-, $-CR_2CR_2-$, $-NRCR_2CR_2NR-$, -NRCR=CRNR- or $-NRCOCR_2NR-$; and/or

wherein each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system and m is 0, 1 or 2.

39. The method of claim 38 wherein the compound of formula (1) is 59-0089, 59-0090, 59-0092 or 59-0094.

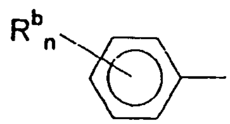
40. The method of claim 31 wherein Ar^1 is

 (6a) or  (7a) or  (8a)

wherein each R^a is a noninterfering substituent and m is 0-4.

41. The method of claim 40 wherein L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, $-NRCR_2-$, $-NRCR_2CR_2-$, $-NRCR_2CO-$, -NRNR-, $-CR_2CR_2-$, $-NRCR_2CR_2NR-$, -NRCR=CRNR- or $-NRCOCR_2NR-$; and/or

Ar^2 is



(v)

,

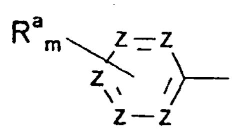
wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or

wherein each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

42. The method of claim 41 wherein the compound of formula (1) is 59-203, 59-285 or 59-286.

43. The method of claim 31 wherein L is a constrained linker.

44. The method of any of claims 1-4 wherein Ar^1 is



(9a)

,

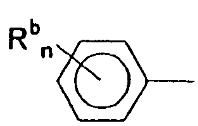
wherein each R^a is independently a noninterfering substituent;

m is an integer of 0-4;

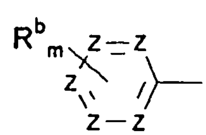
each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be N and at least one Z must be CR.

45. The method of claim 44 wherein L is a flexible conjugating or nonconjugating linker; and/or

wherein Ar^2 is



(v) or



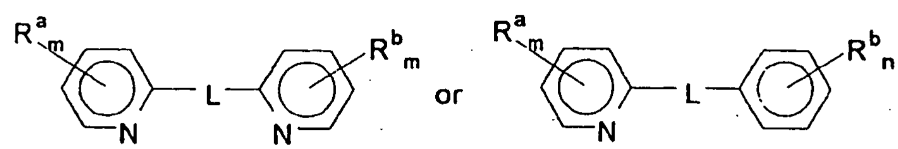
(vi)

,

wherein each R^b is independently a noninterfering substituent, and

in (vi) each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be a N and at least one Z must be CR.

46. The method of claim 45 wherein the compound of formula (1) is of the formula



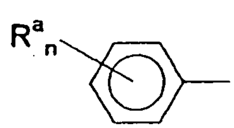
47. The method of claim 46 wherein L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, $-NRCR_2-$, $-NRCR_2CR_2-$, $-NRCR_2CO-$, -NRNR-, $-CR_2CR_2-$, $-NRCR_2CR_2NR-$, -NRCR=CRNR- or $-NRCOCR_2NR-$; and/or

wherein each R^a and R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system and each m and n is independently 0, 1 or 2.

48. The method of claim 47 wherein L is $-NHCR_2CR_2NH-$, m is 1 and R^a is CF_3 para to L.

49. The method of claim 48 wherein the compound of formula (1) is 59-0145, 59-0450, 59-0459 or 59-0483.

50. The method of any of claims 1-4 wherein Ar^1 is



(10a)

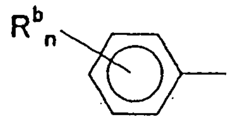
,

wherein each R^a is a noninterfering substituent; and

n is an integer of 0 and 5, and

wherein L is a flexible linker that contains at least one nitrogen; and/or

wherein Ar^2 is of the formula



(v)

and L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, $-NRCR_2-$, $-NRCR_2CR_2-$, $-NRCR_2CO-$, $-NRNRCR_2CR_2-$, -NRNRCR=CR-, $-NRNRCOCR_2-$, -NRNRCOCR=CR-, $-NRNRCSCR_2-$, -NRNRCSCR=CR-, -NRNRCONR-, -NRNRCSNR-, -NRNR-, $-CR_2CR_2-$, $-NRCR_2CR_2NR-$, -NRCR=CRNR- or $-NRCOCR_2NR-$.

51. The method of claim 50 wherein each R^b is independently halo, OR, SR, NR_2, NO, NO_2, OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

52. The method of claim 50 wherein L is -CR=CRCONRNR-, -CR=CRCSNRNR-, $-CR_2CONRNR-$ $-CR_2CSNRNR-$, -NRNRCONR- or -NRNRCSNR- and/or

R^b is $-NR_2$ and n=1 wherein R^b is in the para position.

53. The method of claim 50 wherein R^a is -COOR and m is 1.

54. The method of claim 52 wherein the compound of formula (1) is 59-0045, 59-0095, 59-0096, 59-0097 or 59-0098.

55. A pharmaceutical composition for use in a method to treat a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth replacement and/or an undesirable level of bone resorption which composition contains a pharmaceutically acceptable excipient and an effective amount of a compound of the formula set forth in any preceding claim.

56. A compound for use in preparing a composition for use in the treatment of a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth replacement and/or an undesirable level of bone resorption which method comprises administering said composition to a vertebrate subject, said compound set forth in any preceding claim.

Ar^1 - linker - Ar^2 1.5 - 15Å		(I)
Ar^1	Ar^2	
contains 5-membered heterocycle	substituted or unsubstituted benzene	II-A
contains 5-membered heterocycle	substituted or unsubstituted naphthalene	II-B
contains 5-membered heterocycle	contains 6-membered heterocycle	II-C
contains 5-membered heterocycle	contains 5-membered heterocycle	II-D
contains 6-membered heterocycle	substituted or unsubstituted benzene	II-E
contains 6-membered heterocycle	substituted or unsubstituted naphthalene	II-F
contains 6-membered heterocycle	contains 6-membered heterocycle	II-G
substituted or unsubstituted naphthalene	substituted or unsubstituted benzene	II-H
substituted or unsubstituted naphthalene	substituted or unsubstituted naphthalene	II-I
substituted or unsubstituted benzene	substituted or unsubstituted benzene	II-J

Figure 1

2TJL-C9 CELLS			10/1/96				
5x 10³ Cells/well							
	uM	READ 1	READ 2	AVERAGE	INDUCTION	AVE-BASAL	% MAX
OS-8	100.0000	0.21	0.22	0.22	0.18	-0.99	-17.80
	31.250	3.98	4.44	4.20	3.49	3.00	54.26
	9.766	6.99	6.46	6.72	5.59	5.52	100.00
	3.052	4.62	4.88	4.75	3.95	3.55	64.22
	0.954	3.13	3.16	3.14	2.61	1.94	35.12
	0.298	2.75	2.59	2.67	2.22	1.47	26.58
	0.093	2.10	2.04	2.07	1.72	0.87	15.77
	0.029	1.56	1.71	1.63	1.36	0.43	7.80
	0.0091	1.45	1.42	1.44	1.19	0.23	4.21
	0.0028	1.28	1.37	1.33	1.10	0.12	2.25
	0.0000	1.32	1.30	1.31			
	0.0000	1.20	1.00	1.10			
		AVERAGE BASAL		1.20			

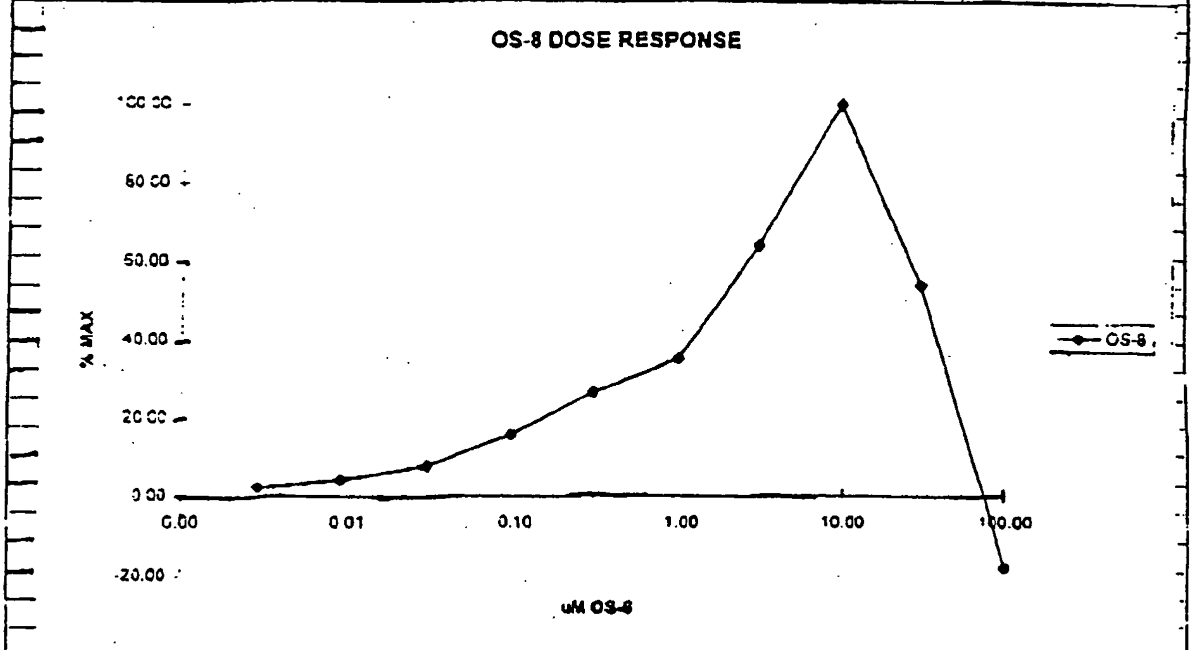


Figure 2

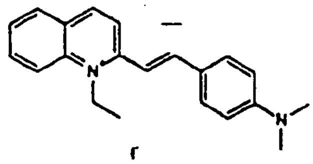
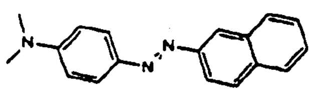
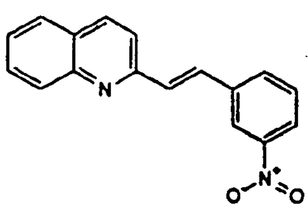
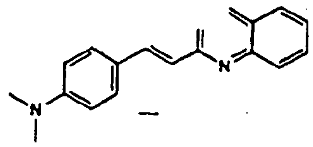
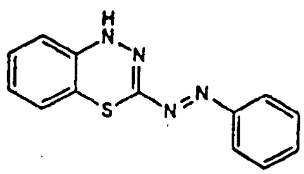
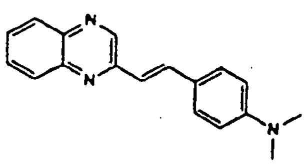
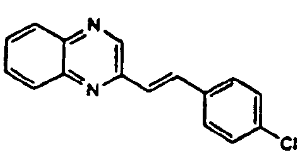
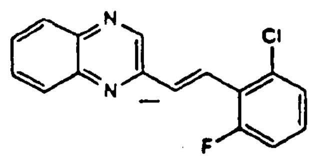
NNC#	MOL.WEIGHT	Concentration		% Response
 50-0194	430.33			
50-0194		100.00	uM	-19.190
		31.25	uM	32.450
		9.77	uM	-14.240
		3.05	uM	-11.330
		953.67	nM	-12.790
		298.02	nM	-13.450
		93.13	nM	-12.290
		29.10	nM	-9.440
		9.09	nM	-6.450
		2.84	nM	-8.130
		888.18	pM	-3.320
 50-0195	275.36			
50-0195		100.00	uM	-4.630
		31.25	uM	16.790
		9.77	uM	62.830
		3.05	uM	102.720
		953.67	nM	60.860
		298.02	nM	32.450
		93.13	nM	19.340
		29.10	nM	17.220
		9.09	nM	5.640
		2.84	nM	4.840
		888.18	pM	5.640
 50-0196	276.30			
50-0196		100.00	uM	-16.210
		31.25	uM	-8.560
		9.77	uM	11.620
		3.05	uM	27.790
		953.67	nM	18.390
		298.02	nM	6.230
		93.13	nM	12.420
		29.10	nM	12.630
		9.09	nM	6.590
		2.84	nM	7.970
		888.18	pM	5.060

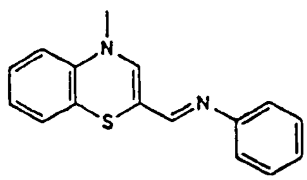
Figure 3

 50-0197		274.37			
50-0197			100.00	uM	-18.250
			31.25	uM	-14.980
			9.77	uM	4.040
			3.05	uM	93.790
			953.67	nM	205.530
			298.02	nM	242.920
			93.13	nM	195.890
			29.10	nM	115.320
			9.09	nM	85.630
			2.84	nM	54.360
			888.18	pM	33.180
 59-0008		254.32			
 59-0019	59-0019				
59-0019			100.00	uM	-22.240
			31.25	uM	-22.670
			9.77	uM	-17.470
			3.05	uM	74.490
			953.67	nM	198.080
			298.02	nM	258.340
			93.13	nM	225.350
			29.10	nM	75.220
			9.09	nM	24.030
			2.84	nM	34.480
			888.18	pM	-3.740
 59-0020		266.73			
59-0020			100.00	uM	-18.510
			31.25	uM	-16.040
			9.77	uM	-0.270
			3.05	uM	96.490
			953.67	nM	153.320
			298.02	nM	110.240
			93.13	nM	60.030

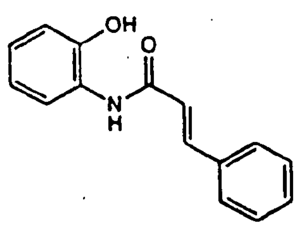
			29.10	nM	37.870
			9.09	nM	24.820
			2.84	nM	20.500
			888.18	pM	13.310



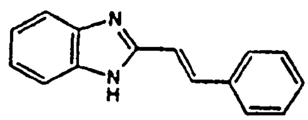
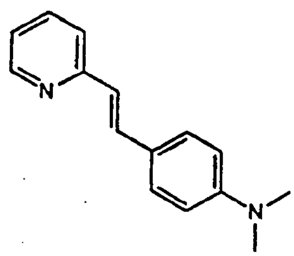
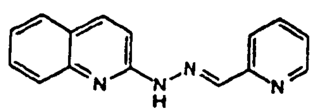
59-0021	284.72		
59-0021		100.00 uM	-16.310
		31.25 uM	-12.850
		9.77 uM	84.130
		3.05 uM	89.940
		953.67 nM	65.750
		298.02 nM	33.940
		93.13 nM	22.560
		29.10 nM	25.020
		9.09 nM	13.910
		2.84 nM	33.270
		888.18 pM	15.500

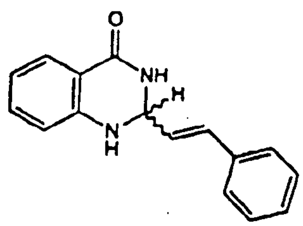


59-0022	266.37		
59-0022		100.00 uM	7.250
		31.25 uM	-2.070
		9.77 uM	-0.270
		3.05 uM	4.390
		953.67 nM	3.060
		298.02 nM	-1.600
		93.13 nM	-0.200
		29.10 nM	-3.270
		9.09 nM	1.130
		2.84 nM	2.590
		888.18 pM	2.460

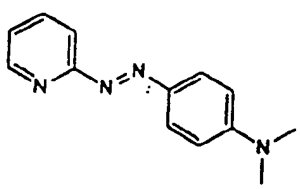


59-0023	239.28		
59-0023		100.00 uM	-12.720
		31.25 uM	33.140
		9.77 uM	56.600
		3.05 uM	29.550
		953.67 nM	25.360
		298.02 nM	15.700
		93.13 nM	7.380
		29.10 nM	-9.710
		9.09 nM	1.000
		2.84 nM	4.520
		888.18 pM	-0.010

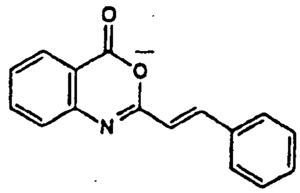
 59-0024	220.28				
 59-0025	224.31				
59-0025		100.00	uM	-25.590	
		31.25	uM	14.150	
		9.77	uM	50.690	
		3.05	uM	57.880	
		953.67	nM	38.900	
		298.02	nM	28.530	
		93.13	nM	19.660	
		29.10	nM	17.490	
		9.09	nM	-0.600	
		2.84	nM	-4.190	
		888.18	pM	4.670	
 59-0026	248.29				
59-0026		100.00	uM	-29.830	
		31.25	uM	-9.440	
		9.77	uM	-10.470	
		3.05	uM	46.220	
		953.67	nM	107.760	
		298.02	nM	86.720	
		93.13	nM	36.850	
		29.10	nM	26.720	
		9.09	nM	8.520	
		2.84	nM	-1.240	
		888.18	pM	4.020	



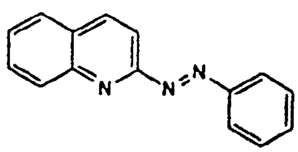
59-0027	250.30				
59-0027		100.00	uM	89.810	
		31.25	uM	54.670	
		9.77	uM	44.940	
		3.05	uM	23.780	
		953.67	nM	8.380	
		298.02	nM	6.330	
		93.13	nM	7.360	
		29.10	nM	3.380	
		9.09	nM	-1.620	
		2.84	nM	-3.670	
		888.18	pM	-0.720	



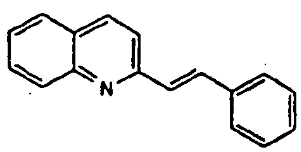
59-0028	226.28				
59-0028		100.00	uM	-26.750	
		31.25	uM	-16.740	
		9.77	uM	29.550	
		3.05	uM	100.580	
		953.67	nM	54.940	
		298.02	nM	31.340	
		93.13	nM	7.500	
		29.10	nM	7.500	
		9.09	nM	7.880	
		2.84	nM	3.140	
		888.18	pM	4.670	



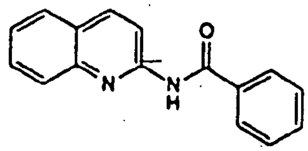
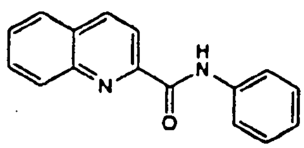
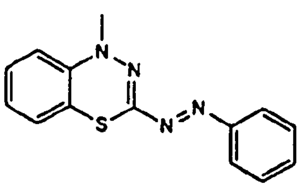
59-0029	249.27				
59-0029		100.00	uM	-15.160	
		31.25	uM	41.940	
		9.77	uM	36.830	
		3.05	uM	7.120	
		953.67	nM	21.880	
		298.02	nM	15.640	
		93.13	nM	1.810	
		29.10	nM	1.370	
		9.09	nM	12.140	
		2.84	nM	-4.230	
		888.18	pM	9.040	

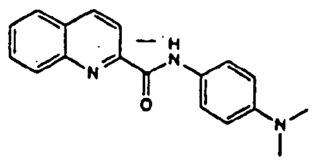
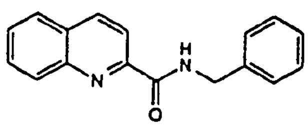
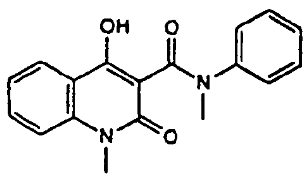


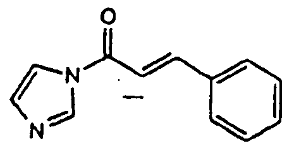
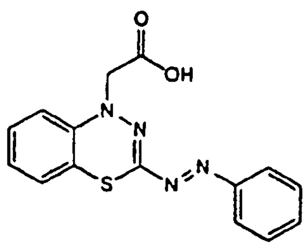
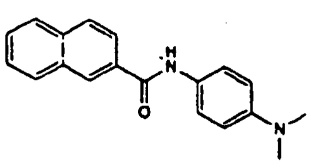
59-0030 A	233.28				
59-0030 A		100.00	uM	-27.970	
		31.25	uM	-22.830	
		9.77	uM	-5.420	
		3.05	uM	57.280	
		953.67	nM	72.620	
		298.02	nM	53.000	
		93.13	nM	29.990	
		29.10	nM	14.630	
		9.09	nM	3.870	
		2.84	nM	6.970	
		888.18	pM	1.810	

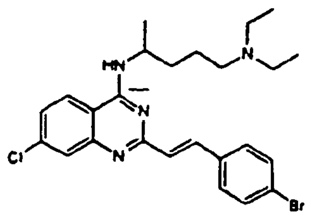
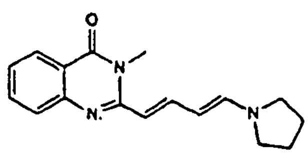
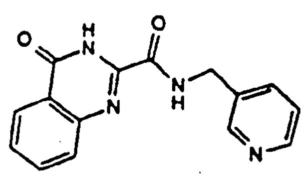


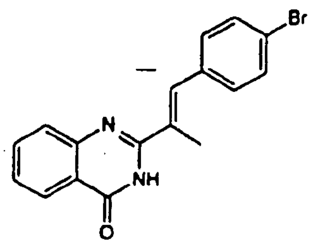
59-0031	231.30				
59-0031		100.00	uM	-25.790	
		31.25	uM	-17.810	
		9.77	uM	20.840	
		3.05	uM	87.380	
		953.67	nM	49.320	
		298.02	nM	43.110	
		93.13	nM	29.630	
		29.10	nM	1.810	
		9.09	nM	1.220	
		2.84	nM	-0.550	
		888.18	pM	4.160	

 59-0032	248.29				
59-0032		100.00	uM	-7.780	
		31.25	uM	40.750	
		9.77	uM	42.820	
		3.05	uM	25.700	
		953.67	nM	31.170	
		298.02	nM	34.410	
		93.13	nM	3.570	
		29.10	nM	4.320	
		9.09	nM	-10.000	
		2.84	nM	5.650	
		888.18	pM	11.990	
 59-0033	248.29				
59-0033		100.00	uM	-28.180	
		31.25	uM	-11.590	
		9.77	uM	55.300	
		3.05	uM	49.710	
		953.67	nM	47.410	
		298.02	nM	0.250	
		93.13	nM	7.980	
		29.10	nM	-8.940	
		9.09	nM	-7.630	
		2.84	nM	-0.400	
		888.18	pM	-5.980	
 59-0034	268.34				
59-0034		100.00	uM	-28.51	
		31.25	uM	24	
		9.77	uM	73.58	
		3.05	uM	37.91	
		953.67	nM	20.09	
		298.02	nM	16.87	
		93.13	nM	15.23	
		29.10	nM	28.83	
		9.09	nM	9.08	
		2.84	nM	23.02	
		888.18	pM	-0.32	

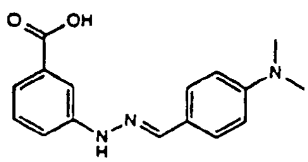
 59-0035	291.36			
59-0035		100.00	uM	-14.92
		31.25	uM	29.17
		9.77	uM	15.87
		3.05	uM	16.8
		953.67	nM	3.88
		298.02	nM	6.15
		93.13	nM	3.22
		29.10	nM	-10.03
		9.09	nM	15.58
		2.84	nM	-3.56
		888.18	pM	-7.13
 59-0036	262.31			
59-0036		100.00	uM	-0.98
		31.25	uM	-3.25
		9.77	uM	-4.54
		3.05	uM	-1.95
		953.67	nM	0.32
		298.02	nM	-6.49
		93.13	nM	-17.19
		29.10	nM	-0.66
		9.09	nM	-5.52
		2.84	nM	-9.4
		888.18	pM	-16.53
 59-0037	308.00			
59-0037		100.00	uM	-10.69
		31.25	uM	-11.99
		9.77	uM	-10.03
		3.05	uM	-19.11
		953.67	nM	-9.4
		298.02	nM	2.27
		93.13	nM	-2.9
		29.10	nM	-10.69
		9.09	nM	2.59
		2.84	nM	0.66
		888.18	pM	-2.59

 59-0038	291.36			
59-0038		100.00	uM	-23.430
		31.25	uM	-8.390
		9.77	uM	-0.100
		3.05	uM	-2.860
		953.67	nM	-2.240
		298.02	nM	3.900
		93.13	nM	6.350
		29.10	nM	1.150
		9.09	nM	6.960
		2.84	nM	-4.390
		888.18	pM	-0.380
 59-0039	312.35			
59-0039		100.00	uM	14.170
		31.25	uM	7.620
		9.77	uM	1.940
		3.05	uM	-3.140
		953.67	nM	-7.770
		298.02	nM	-5.980
		93.13	nM	-8.820
		29.10	nM	-2.390
		9.09	nM	-16.580
		2.84	nM	-4 480
		888.18	pM	-0.450
 59-0040	290.37			
59-0040		100.00	uM	-20 400
		31.25	uM	-17.310
		9.77	uM	-8.110
		3.05	uM	32.180
		953.67	nM	36.180
		298.02	nM	17.440
		93.13	nM	2.040
		29.10	nM	10.350
		9.09	nM	-6.070
		2.84	nM	6.960
		888.18	pM	13.440

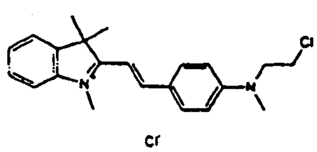
 59-0041	501.90			
59-0041		100.00	uM	-18.37
		31.25	uM	-17.33
		9.77	uM	-5.11
		3.05	uM	3.31
		953.67	nM	-0.77
		298.02	nM	-1.56
		93.13	nM	3.55
		29.10	nM	-11.24
		9.09	nM	0.25
		2.84	nM	-0.27
		888.18	pM	2.02
 59-0042	281.36			
59-0042		100.00	uM	163.51
		31.25	uM	-7.67
		9.77	uM	9.41
		3.05	uM	0.75
		953.67	nM	6.11
		298.02	nM	3.82
		93.13	nM	2.54
		29.10	nM	4.07
		9.09	nM	-9.73
		2.84	nM	-0.02
		888.18	pM	18.37
 59-0043	280.29			
59-0043		100.00	uM	20.66
		31.25	uM	7.4
		9.77	uM	-1.29
		3.05	uM	-2.31
		953.67	nM	1.54
		298.02	nM	-0.79
		93.13	nM	1.52
		29.10	nM	2.79
		9.09	nM	-0.27
		2.84	nM	8.92
		888.18	pM	-4.34



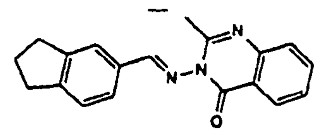
59-0044	341.21				
59-0044		100.00	uM	7.38	
		31.25	uM	11.72	
		9.77	uM	12.49	
		3.05	uM	-0.52	
		953.67	nM	0.5	
		298.02	nM	6.11	
		93.13	nM	-1.54	
		29.10	nM	19.14	
		9.09	nM	7.13	
		2.84	nM	-2.06	
		888.18	pM	5.84	



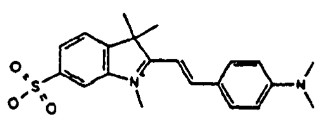
59-0045	283.33				
59-0045		100.00	uM	52.37	64.460
		31.25	uM	148.43	192.960
		9.77	uM	204.47	422.540
		3.05	uM	280.3	437.020
		953.67	nM	254.62	410.890
		298.02	nM	218.21	266.090
		93.13	nM	196.98	183.730
		29.10	nM	96.06	80.440
		9.09	nM	67.35	55.530
		2.84	nM	52.99	44.160



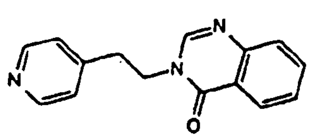
59-0046	389.37				
59-0046		100.00	uM	79.33	
		31.25	uM	2.24	
		9.77	uM	-1.67	
		3.05	uM	-6.18	
		953.67	nM	0.001	
		298.02	nM	-3.63	
		93.13	nM	-0.84	
		29.10	nM	-6.42	
		9.09	nM	-3.92	
		2.84	nM	0.3	
		888.18	pM	5.61	



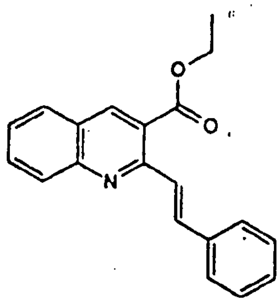
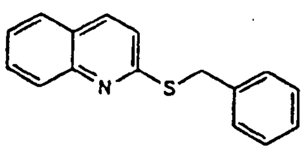
59-0047	303.37			
59-0047		100.00	uM	-6.73
		31.25	uM	10.38
		9.77	uM	-6.16
		3.05	uM	-1.39
		953.67	nM	-10.11
		298.02	nM	-4.49
		93.13	nM	-7.28
		29.10	nM	-12.34
		9.09	nM	-3.08
		2.84	nM	-2.26
		888.18	pM	-5.34

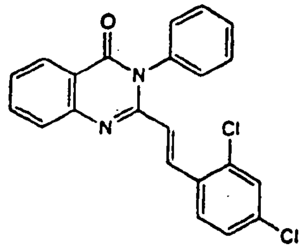


59-0048	384.50			
59-0048		100.00	uM	-6.73
		31.25	uM	0.27
		9.77	uM	-5.61
		3.05	uM	-2.26
		953.67	nM	-12.89
		298.02	nM	-1.69
		93.13	nM	-4.77
		29.10	nM	-8.14
		9.09	nM	-3.92
		2.84	nM	-11.2
		888.18	pM	-4.77

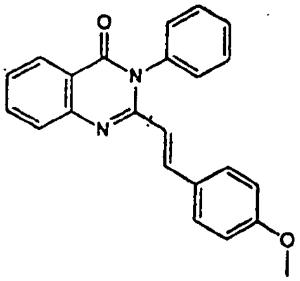


59-0049	251.29			
59-0049		100.00	uM	4.49
		31.25	uM	0
		9.77	uM	-4.77
		3.05	uM	1.96
		953.67	nM	8.69
		298.02	nM	-5.04
		93.13	nM	-2.24
		29.10	nM	1.69
		9.09	nM	-4.49
		2.84	nM	2.24
		888.18	pM	-0.31

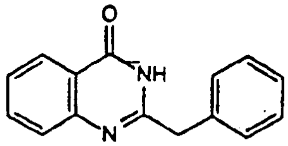
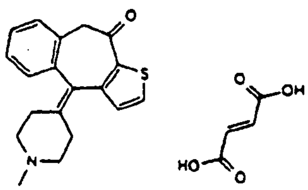
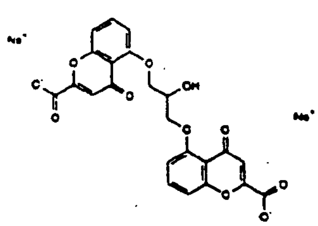
 59-0050	303.36				
59-0050		100.00	uM	45.79	
		31.25	uM	10.02	
		9.77	uM	11.29	
		3.05	uM	-4.68	
		953.67	nM	-6.92	
		298.02	nM	-5.65	
		93.13	nM	1.69	
		29.10	nM	-7.57	
		9.09	nM	-12.05	
		2.84	nM	-13.63	
		888.18	pM	5.2	
 59-0051	251.35				
59-0051		100.00	uM	32.36	
		31.25	uM	-18.42	
		9.77	uM	-0.55	
		3.05	uM	-13.94	
		953.67	nM	-12.02	
		298.02	nM	-14.59	
		93.13	nM	-7.55	
		29.10	nM	-11.4	
		9.09	nM	-14.91	
		2.84	nM	-10.74	
		888.18	pM	-20.03	

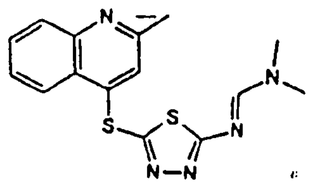


59-0052	393.28			
59-0052		100.00	uM	-21.62
		31.25	uM	-13.32
		9.77	uM	-21.31
		3.05	uM	-11.08
		953.67	nM	-20.66
		298.02	nM	-17.14
		93.13	nM	-16.49
		29.10	nM	-11.4
		9.09	nM	-10.74
		2.84	nM	-11.08
		888.18	pM	-14.59



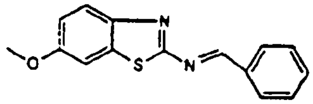
59-0053	354.41			
59-0053		100.00	uM	-17.14
		31.25	uM	-21.31
		9.77	uM	-9.47
		3.05	uM	-11.08
		953.67	nM	-0.83
		298.02	nM	-11.4
		93.13	nM	-9.47
		29.10	nM	-19.72
		9.09	nM	-18.45
		2.84	nM	-10.09
		888.18	pM	-2.76

 59-0054	236.28				
59-0054		100.00	uM	-20.04	
		31.25	uM	-6.95	
		9.77	uM	8.3	
		3.05	uM	-3.37	
		953.67	nM	-2.4	
		298.02	nM	-0.99	
		93.13	nM	-0.99	
		29.10	nM	-1.94	
		9.09	nM	5.92	
		2.84	nM	-2.17	
		888.18	pM	-9.31	
 59-0055	425.51				
59-0055		100.00	uM	-13.76	
		31.25	uM	-9.51	
		9.77	uM	-2.02	
		3.05	uM	3.24	
		953.67	nM	-6.27	
		298.02	nM	-4.05	
		93.13	nM	-1.62	
		29.10	nM	-7.49	
		9.09	nM	-7.09	
		2.84	nM	-3.04	
 59-0056	512.34				
59-0056		100.00	uM	-1.42	
		31.25	uM	-4.87	
		9.77	uM	0.18	
		3.05	uM	3.84	
		953.67	nM	-5.07	
		298.02	nM	-7.29	
		93.13	nM	0.001	
		29.10	nM	-4.25	
		9.09	nM	-1.02	
		2.84	nM	-3.85	



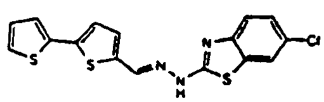
59-0057

59-0057	100.00	uM	-24.150
	31.25	uM	-24.300
	9.77	uM	-5.960
	3.05	uM	-11.500
	953.67	nM	-13.000
	298.02	nM	-6.280
	93.13	nM	-12.550
	29.10	nM	-6.870
	9.09	nM	-8.520
	2.84	nM	-16.290



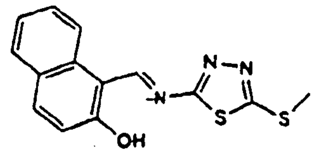
59-0058

59-0058	100.00	uM	4.170
	31.25	uM	7.620
	9.77	uM	-1.790
	3.05	uM	-7.320
	953.67	nM	-1.940
	298.02	nM	-6.870
	93.13	nM	-1.490
	29.10	nM	-8.370
	9.09	nM	-5.080
	2.84	nM	-12.400



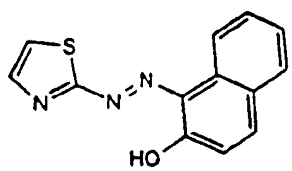
59-0059

59-0059	100.00	uM	-18.770
	31.25	uM	-16.140
	9.77	uM	-3.090
	3.05	uM	0.150
	953.67	nM	6.010
	298.02	nM	-1.910
	93.13	nM	-1.760
	29.10	nM	-9.100
	9.09	nM	-8.220
	2.84	nM	-5.720



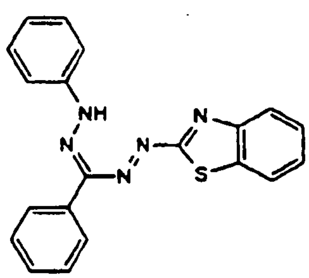
59-0060

59-0060		100.00	uM	-4.250
		31.25	uM	-14.520
		9.77	uM	1.030
		3.05	uM	-1.180
		953.67	nM	-13.200
		298.02	nM	-0.740
		93.13	nM	-3.670
		29.10	nM	-7.340
		9.09	nM	-1.310
		2.84	nM	0.290



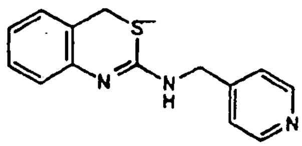
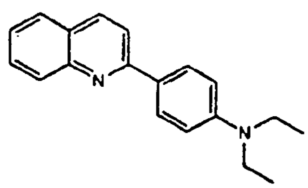
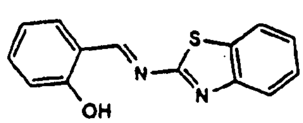
59-0061

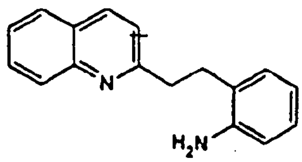
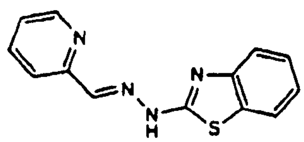
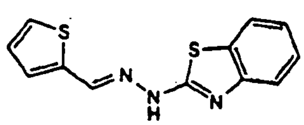
59-0061		100.00	uM	-17.890
		31.25	uM	-16.770
		9.77	uM	-17.170
		3.05	uM	-14.080
		953.67	nM	-17.020
		298.02	nM	-7.190
		93.13	nM	-1.910
		29.10	nM	-0.440
		9.09	nM	-6.010
		2.84	nM	-4 560

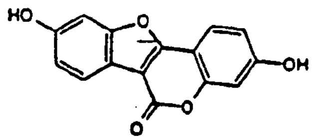
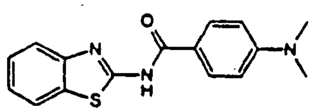
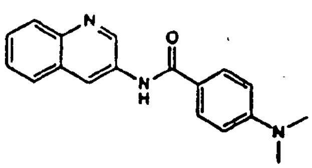


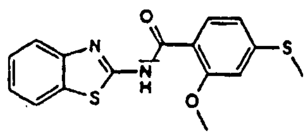
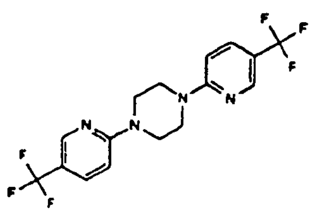
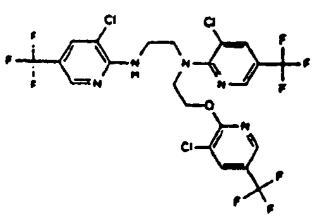
59-0062

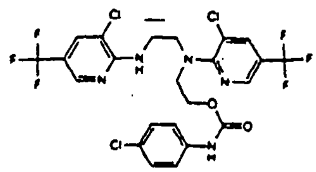
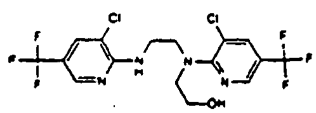
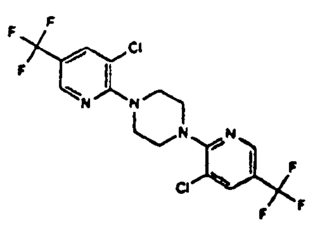
59-0062		100.00	uM	-13.940
		31.25	uM	-12.910
		9.77	uM	-4.560
		3.05	uM	-4.540
		953.67	nM	-6.900
		298.02	nM	-4 100
		93.13	nM	-1.620
		29.10	nM	3.230

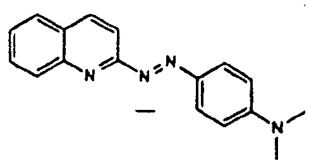
		9.09	nM	8.070
		2.84	nM	0.440
 59-0063				
59-0063		100.00	uM	-2.510
		31.25	uM	-6.130
		9.77	uM	-8.950
		3.05	uM	-8.020
		953.67	nM	-8.010
		298.02	nM	-2.520
		93.13	nM	-5.810
		29.10	nM	-3.450
		9.09	nM	-4.390
		2.84	nM	-6.280
 59-0064				
59-0064		100.00	uM	-23.090
		31.25	uM	-21.040
		9.77	uM	78.400
		3.05	uM	155.220
		953.67	nM	113.120
		298.02	nM	30.640
		93.13	nM	15.240
		29.10	nM	22.150
		9.09	nM	-0.770
		2.84	nM	4.410
 59-0065				
59-0065		100.00	uM	-2.030
		31.25	uM	-2.980
		9.77	uM	-15.240
		3.05	uM	-15.400
		953.67	nM	-15.240
		298.02	nM	-10.520
		93.13	nM	-13.830
		29.10	nM	-5.810
		9.09	nM	-3.620
		2.84	nM	-7.070

 59-0066				
59-0066		100.00	uM	10.060
		31.25	uM	2.680
		9.77	uM	10.850
		3.05	uM	14.610
		953.67	nM	0.950
		298.02	nM	3.780
		93.13	nM	1.730
		29.10	nM	-2.820
		9.09	nM	-2.820
		2.84	nM	-3.920
 59-0067				
59-0067		100.00	uM	-24.040
		31.25	uM	-24.890
		9.77	uM	-1.450
		3.05	uM	60.900
		953.67	nM	133.860
		298.02	nM	75.330
		93.13	nM	28.760
		29.10	nM	20.070
		9.09	nM	4.980
		2.84	nM	4.450
 59-0068				
59-0068		100.00	uM	-22.130
		31.25	uM	-7.880
		9.77	uM	93.900
		3.05	uM	81.060
		953.67	nM	22.330
		298.02	nM	17.300
		93.13	nM	8.460
		29.10	nM	-3.530
		9.09	nM	-4.230
		2.84	nM	-6.140

 59-0069					
59-0069		100.00	uM		5.490
		31.25	uM		9.670
		9.77	uM		16.090
		3.05	uM		-7.180
		953.67	nM		-2.840
		298.02	nM		-3.710
		93.13	nM		-11.180
		29.10	nM		-5.790
		9.09	nM		-7.180
		2.84	nM		-4.750
 59-0070					
59-0070		100.00	uM		-25.930
		31.25	uM		-23.000
		9.77	uM		36.060
		3.05	uM		214.280
		953.67	nM		158.530
		298.02	nM		72.890
		93.13	nM		20.940
		29.10	nM		7.760
		9.09	nM		7.590
		2.84	nM		-8.400
 59-0071					
59-0071		100.00	uM		-18.650
		31.25	uM		-15.540
		9.77	uM		17.060
		3.05	uM		176.090
		953.67	nM		76.070
		298.02	nM		31.260
		93.13	nM		16.410
		29.10	nM		4.870
		9.09	nM		-7.330
		2.84	nM		-4.660

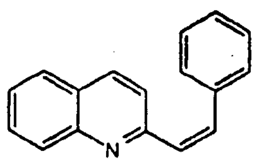
 59-0072					
59-0072		100.00	uM	-19.750	
		31.25	uM	-18.650	
		9.77	uM	-18.430	
		3.05	uM	-15.770	
		953.67	nM	9.970	
		298.02	nM	74.740	
		93.13	nM	175.430	
		29.10	nM	213.580	
		9.09	nM	164.320	
		2.84	nM	119.100	
		888.18	pM	60.770	
 59-0073					
59-0073		100.00	uM	-3.010	
		31.25	uM	-4.830	
		9.77	uM	-9.660	
		3.05	uM	-4.680	
		953.67	nM	-6.500	
		298.02	nM	-2.510	
		93.13	nM	7.140	
		29.10	nM	0.97	
		9.09	nM	-5.5	
		2.84	nM	5.3	
 59-0074					
59-0074		100.00	uM	-2.85	
		31.25	uM	2.14	
		9.77	uM	-4.85	
		3.05	uM	-3.5	
		953.67	nM	-4.85	
		298.02	nM	9.95	
		93.13	nM	4.47	
		29.10	nM	-8	
		9.09	nM	-4.17	
		2.84	nM	6.97	

 59-0075					
59-0075		100.00	uM		-0.68
		31.25	uM		-10.16
		9.77	uM		-5.35
		3.05	uM		-6.5
		953.67	nM		-0.85
		298.02	nM		5.97
		93.13	nM		0.97
		29.10	nM		-2.35
		9.09	nM		0.32
		2.84	nM		10.47
 59-0076					
59-0076		100.00	uM		-19.12
		31.25	uM		9.29
		9.77	uM		10.63
		3.05	uM		22.43
		953.67	nM		19.93
		298.02	nM		3.47
		93.13	nM		19.93
		29.10	nM		10.63
		9.09	nM		14.28
		2.84	nM		11.3
 59-0077					
59-0077		100.00	uM		-20.96
		31.25	uM		-16.23
		9.77	uM		-10.58
		3.05	uM		-11.96
		953.67	nM		-19.44
		298.02	nM		-17.3
		93.13	nM		-13.79
		29.10	nM		-15.62
		9.09	nM		-14.09
		2.84	nM		-14.4



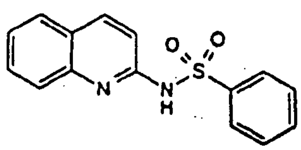
59-0078

	100.00 uM	-26.540
	31.25 uM	-22.560
	9.77 uM	71.530
	3.05 uM	207.960
	953.67 nM	379.230
	298.02 nM	241.460
	93.13 nM	136.100
	29.10 nM	84.020
	9.09 nM	50.350
	2.84 nM	56.600
	0.80 nM	92.520



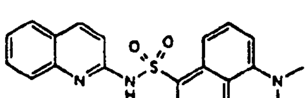
59-0079

59-0079	100.00 uM	-34.980
	31.25 uM	-21.390
	9.77 uM	37.200
	3.05 uM	122.580
	953.67 nM	69.010
	298.02 nM	64.000
	93.13 nM	46.490
	29.10 nM	30.310
	9.09 nM	33.490
	2.84 nM	29.760

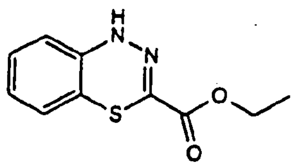
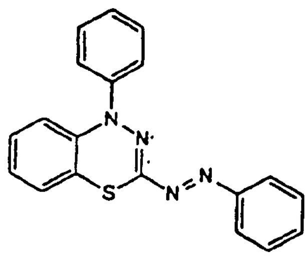
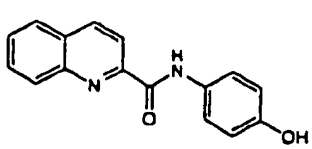


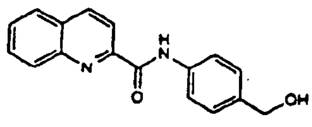
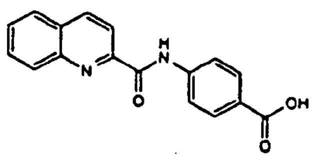
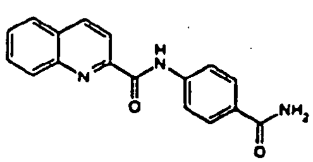
59-0080

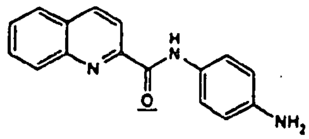
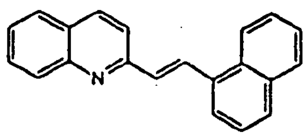
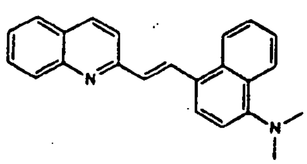
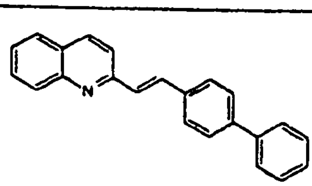
59-0080	100.00 uM	5.390
	31.25 uM	5.560
	9.77 uM	6.440
	3.05 uM	2.440
	953.67 nM	-5.030
	298.02 nM	7.660
	93.13 nM	-3.630
	29.10 nM	3.650
	9.09 nM	1.050
	2.84 nM	6.940



59-0081

59-0081	100.00	uM	62.840
	31.25	uM	11.300
	9.77	uM	-8.670
	3.05	uM	2.440
	953.67	nM	-5.200
	298.02	nM	-2.080
	93.13	nM	1.220
	29.10	nM	-2.250
	9.09	nM	1.050
	2.84	nM	-3.300
 59-0082			
59-0082	100.00	uM	111.79
	31.25	uM	62.68
	9.77	uM	32.38
	3.05	uM	9.11
	953.67	nM	-10.62
	298.02	nM	-1.66
	93.13	nM	-6.89
	29.10	nM	-3.91
	9.09	nM	2.22
	2.84	nM	16.36
 59-0083			
59-0083	100.00	uM	48.93
	31.25	uM	40.91
	9.77	uM	25.85
	3.05	uM	17.65
	953.67	nM	8.55
	298.02	nM	3.9
	93.13	nM	2.05
	29.10	nM	7.99
	9.09	nM	-3.91
	2.84	nM	3.35
 59-0084			
59-0084	100.00	uM	37.670
	31.25	uM	26.050
	9.77	uM	9.210
	3.05	uM	10.070

		953.67 nM	21.700
		298.02 nM	5.900
		93.13 nM	4.870
		29.10 nM	-10.920
		9.09 nM	10.080
		2.84 nM	-2.080
 59-0085			
59-0085		100.00 uM	17.070
		31.25 uM	41.890
		9.77 uM	18.500
		3.05 uM	20.340
		953.67 nM	22.490
		298.02 nM	8.090
		93.13 nM	11.790
		29.10 nM	1.240
		9.09 nM	-0.760
		2.84 nM	5.940
 59-0086			
59-0086		100.00 uM	30.750
		31.25 uM	31.190
		9.77 uM	14.790
		3.05 uM	13.500
		953.67 nM	14.080
		298.02 nM	3.940
		93.13 nM	9.370
		29.10 nM	-2.610
		9.09 nM	-5.040
		2.84 nM	1.530
 59-0087			
59-0087		100.00 uM	10.660
		31.25 uM	11.080
		9.77 uM	3.100
		3.05 uM	-1.320
		953.67 nM	17.070
		298.02 nM	7.950
		93.13 nM	-4.460
		29.10 nM	4.510
		9.09 nM	-0.470
		2.84 nM	9.660

 59-0088			
59-0088		100.00|uM	
		31.25|uM	
		9.77|uM	
		3.05|uM	
		953.67|nM	
		298.02|nM	
		93.13|nM	
		29.10|nM	
		9.09|nM	
		2.84|nM	
 59-0089			
59-0089		100.00|uM	60.09|
		31.25|uM	116.25|
		9.77|uM	65.84|
		3.05|uM	36.1|
		953.67|nM	37.96|
		298.02|nM	18.42|
		93.13|nM	6.33|
		29.10|nM	13.58|
		9.09|nM	0.75|
		2.84|nM	-5.77|
 59-0090			
59-0090		100.00|uM	32.77|
		31.25|uM	24.63|
		9.77|uM	19.5|
		3.05|uM	41.31|
		953.67|nM	9.8|
		298.02|nM	-1.76|
		93.13|nM	3.53|
		29.10|nM	2.95|
		9.09|nM	2.95
		2.84|nM	7.8|
 59-0091			
59-0091		100.00|uM	0.26|
		31.25|uM	13.54

		9.77	uM	95.94	
		3.05	uM	87.71	
		953.67	nM	44.17	
		298.02	nM	38.26	
		93.13	nM	23.87	
		29.10	nM	21.65	
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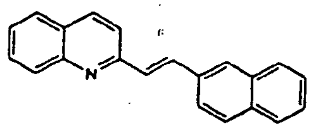
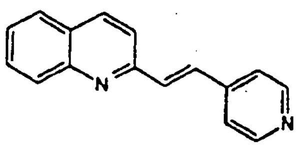
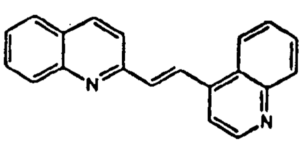
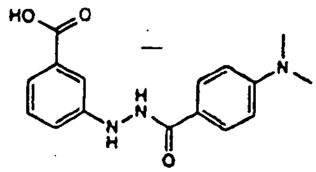
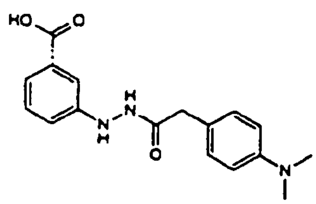
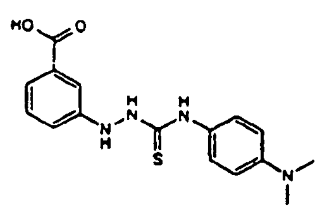
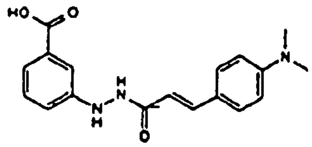
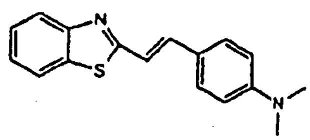
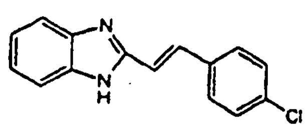
		2.84	nM	20.92	
 59-0092					
59-0092					
		100.00	uM	-11.56	
		31.25	uM	17.84	
		9.77	uM	50.19	
		3.05	uM	25.84	
		953.67	nM	14.41	
		298.02	nM	6.77	
		93.13	nM	8.62	
		29.10	nM	2.22	
		9.09	nM	6.38	
		2.84	nM	1	
 59-0093					
59-0093					
		100.00	uM	-11.67	
		31.25	uM	15.02	
		9.77	uM	35.44	
		3.05	uM	29.89	
		953.67	nM	22.88	
		298.02	nM	19.56	
		93.13	nM	5.18	
		29.10	nM	7.39	
		9.09	nM	4.56	
		2.84	nM	5.9	
 59-0094					
59-0094					
		100.00	uM	-17.69	
		31.25	uM	45.15	
		9.77	uM	24.97	
		3.05	uM	19.81	
		953.67	nM	9.35	
		298.02	nM	1.36	
		93.13	nM	9.24	
		29.10	nM	-0.48	
		9.09	nM	6.16	
		2.84	nM	1.61	

 59-0095						
59-0095			100.00	uM		44.7
			31.25	uM		47.61
			9.77	uM		12.78
			3.05	uM		21.49
			953.67	nM		15.01
			298.02	nM		10.22
			93.13	nM		13.98
			29.10	nM		20.31
			9.09	nM		10.9
			2.84	nM		9.21
 59-0096						
59-0096			100.00	uM		413.05
			31.25	uM		287.23
			9.77	uM		137.38
			3.05	uM		78.5
			953.67	nM		49.13
			298.02	nM		50.68
			93.13	nM		47.95
			29.10	nM		26.28
			9.09	nM		18.75
			2.84	nM		22.17
 59-0097						
59-0097			100.00	uM		77.47
			31.25	uM		201.9
			9.77	uM		160.93
			3.05	uM		61.44
			953.67	nM		47.78
			298.02	nM		51.54
			93.13	nM		34.64
			29.10	nM		43.18
			9.09	nM		39.91
			2.84	nM		27.13

 59-0098					
59-0098		100.00 uM			-1.38
		31.25 uM			166.69
		9.77 uM			221.7
		3.05 uM			164.69
		953.67 nM			96.94
		298.02 nM			68.25
		93.13 nM			57
		29.10 nM			51.88
		9.09 nM			41.29
		2.84 nM			33.43
 59-0099					
59-0099		100.00 uM		13.040	
		31.25 uM		56.880	
		9.77 uM		119.340	
		3.05 uM		237.420	
		953.67 nM		285.440	
		298.02 nM		164.610	
		93.13 nM		123.300	
		29.10 nM		69.240	
		9.09 nM		44.500	
		2.84 nM		47.390	
 59-0100					
59-0100		100.00 uM		-10.020	
		31.25 uM		-10.730	
		9.77 uM		30.340	
		3.05 uM		114.410	
		953.67 nM		77.540	
		298.02 nM		40.290	
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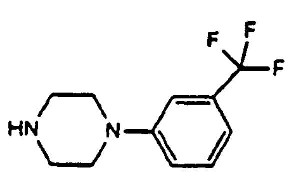
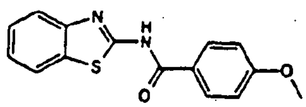
		9.09 nM		17.480	
		2.84 nM		11.470	
 59-0101					
59-0101		100.00 uM		26.370	

		31.25	uM	12.440
		9.77	uM	-0.780
		3.05	uM	10.280
		953.67	nM	2.110
		298.02	nM	7.860
		93.13	nM	1.140
		29.10	nM	2.820
		9.09	nM	4.150
		2.84	nM	5.590
 59-0102	284.34			
59-0102		100.00	uM	-24.350
		31.25	uM	-11.140
		9.77	uM	63.640
		3.05	uM	121.320
		953.67	nM	79.530
		298.02	nM	72.460
		93.13	nM	66.290
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		9.09	nM	27.260
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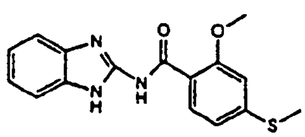
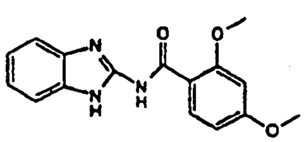
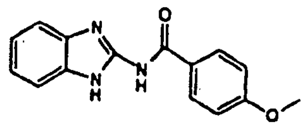
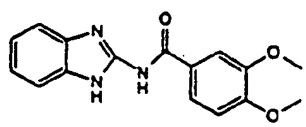
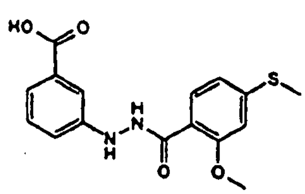
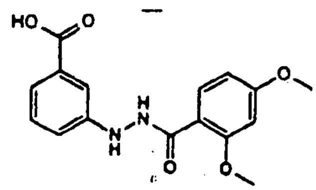
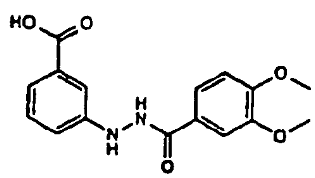
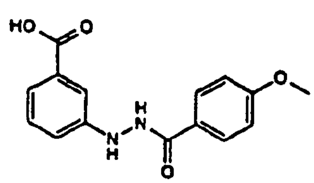
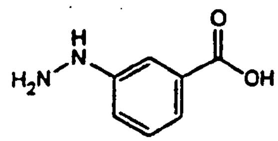
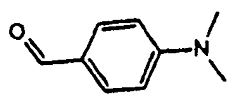
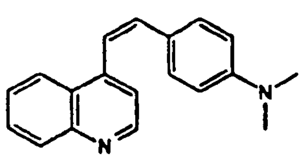
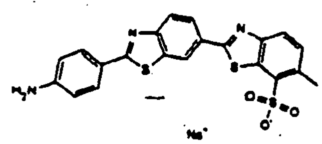
 59-0103	313.38			
		100.00	uM	-29.69
		31.25	uM	-29.53
		9.77	uM	-28.22
		3.05	uM	-27.72
		953.67	nM	-5.58
		298.02	nM	54.15
		93.13	nM	170.95
		29.10	nM	222.87
		9.09	nM	210.39
		2.84	nM	203.4
		0.80	nM	114.55
 59-0104	297.31			
		100.00	uM	-29.84
		31.25	uM	-28.72
		9.77	uM	-29.2
		3.05	uM	-27.05
		953.67	nM	24.37
		298.02	nM	196.42
		93.13	nM	213.89

		29.10	nM	220.04
		9.09	nM	245.42
		2.84	nM	182.45
		0.80	nM	119.55
 59-0105	267.29			
		100.00	uM	-25.72
		31.25	uM	-15.89
		9.77	uM	31.7
		3.05	uM	54.17
		953.67	nM	53.67
		298.02	nM	41.35
		93.13	nM	44.6
		29.10	nM	39.02
		9.09	nM	25.38
		2.84	nM	31.7
		0.80	nM	18.05
 59-0106	297.31			
		100.00	uM	-14.05
		31.25	uM	223.52
		9.77	uM	202.58
		3.05	uM	107.73
		953.67	nM	71.3
		298.02	nM	44.84
		93.13	nM	26.54
		29.10	nM	23.05
		9.09	nM	27.87
		2.84	nM	12.23
		0.80	nM	11.4
 59-0107	332.38			
		100.00	uM	48.55
		31.25	uM	22.87
		9.77	uM	7.19
		3.05	uM	0.65
		953.67	nM	-11.12
		298.02	nM	-3.92
		93.13	nM	1.09
		29.10	nM	-15.69

		9.09	nM	[illegible]
		2.84	nM	-2.62
		0.80	nM	-16.11
 59-0108	316.31			
		100.00	uM	227.73
		31.25	uM	96.02
		9.77	uM	58.57
		3.05	uM	37.23
		953.67	nM	18.94
		298.02	nM	25.68
		93.13	nM	-4.8
		29.10	nM	2.62
		9.09	nM	-4.8
		2.84	nM	3.92
		0.80	nM	4.14
 59-0109	316.31			
		100.00	uM	43.12
		31.25	uM	27.64
		9.77	uM	5.89
		3.05	uM	6.32
		953.67	nM	13.51
		298.02	nM	7.85
		93.13	nM	3.71
		29.10	nM	-3.27
		9.09	nM	5.01
		2.84	nM	-4.58
		0.80	nM	6.98
 59-0110	286.29			
		100.00	uM	65.11
		31.25	uM	67.05
		9.77	uM	-35.27
		3.05	uM	25.26
		953.67	nM	27.01
		298.02	nM	15.24

		93.13	nM	0.68
		29.10	nM	5.89
		9.09	nM	5.45
		2.84	nM	10.24
		0.80	nM	4.14
 59-0111	152.15			
		100.00	uM	23.360
		31.25	uM	22.330
		9.77	uM	12.260
		3.05	uM	5.390
		953.67	nM	2.190
		298.02	nM	1.230
		93.13	nM	2.430
		29.10	nM	6.350
		9.09	nM	4.350
		2.84	nM	4.350
		0.80	nM	3.230
 59-0112	149.19			
		100.00	uM	2.670
		31.25	uM	4.670
		9.77	uM	2.750
		3.05	uM	3.790
		953.67	nM	4.270
		298.02	nM	1.150
		93.13	nM	9.630
		29.10	nM	0.920
		9.09	nM	0.510
		2.84	nM	12.900
		0.80	nM	2.990
 59-0113	274.37			
		100.00	uM	22.010
		31.25	uM	25.940
		9.77	uM	7.500
		3.05	uM	3.070
		953.67	nM	-0.760
		298.02	nM	-4.690
		93.13	nM	-4.790
		29.10	nM	5.090
		9.09	nM	0.150
		2.84	nM	-0.250
		0.80	nM	0.150

 59-0114	475.54			
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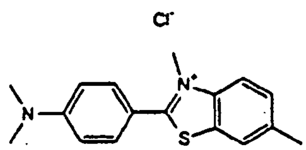
		31.25	uM	36.120
		9.77	uM	25.840
		3.05	uM	16.670
		953.67	nM	12.540
		298.02	nM	9.420
		93.13	nM	-1.060
		29.10	nM	2.160
		9.09	nM	-6.000
		2.84	nM	2.470
		0.80	nM	-1.460
 59-0115	318.87			
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		9.77	uM	-10.430
		3.05	uM	-12.340
		953.67	nM	-13.750
		298.02	nM	-13.960
		93.13	nM	-11.940
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		9.09	nM	-8.820
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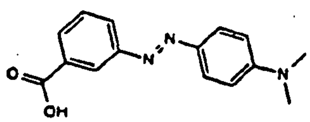
		0.80	nM	-0.050
 59-0116	269.30			
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		9.77	uM	231.070
		3.05	uM	240.670
		953.67	nM	132.020
		298.02	nM	75.820
		93.13	nM	63.250
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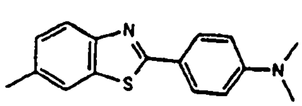
		9.09	nM	39.440
		2.84	nM	42.170
		0.80	nM	31.160
 59-0117	268.38			
		100.00	uM	-68.520

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		9.77	uM	111.630
		3.05	uM	64.340
		953.67	nM	4.740
		298.02	nM	-19.270
		93.13	nM	-26.660
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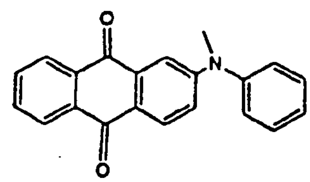
		9.09	nM	-42.180
		2.84	nM	-41.300
		0.80	nM	-39.220
 59-0118	313.36			
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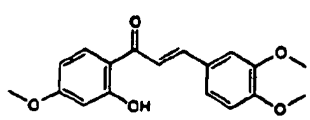
		31.25	uM	-56.580
		9.77	uM	-58.060
		3.05	uM	-55.720
		953.67	nM	-48.200
		298.02	nM	-50.300
		93.13	nM	-33.310
		29.10	nM	-47.340
		9.09	nM	-49.310
		2.84	nM	-56.200
		0.80	nM	-57.310
 59-0119	314.34			
		100.00	uM	167.500
		31.25	uM	-29.240
		9.77	uM	-57.800
		3.05	uM	-52.030
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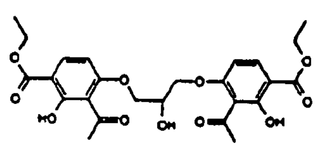
		298.02	nM	-53.870
		93.13	nM	-38.110
		29.10	nM	-55.100
		9.09	nM	-52.270
		2.84	nM	-53.500
		0.80	nM	-43.650
 59-0120	504.49			
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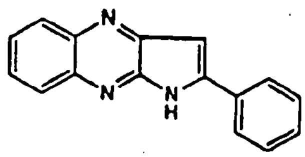
		31.25	uM	-80.470
		9.77	uM	-66.800
		3.05	uM	-80.790
		953.67	nM	-54.240
		298.02	nM	-45.250
		93.13	nM	-50.660

		29.10	nM	-50.300
		9.09	nM	-50.300
		2.84	nM	-50.300
		0.80	nM	-43.280
 59-0121	245.29			
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		31.25	uM	-75.590
		9.77	uM	25.650
		3.05	uM	94.850
		953.67	nM	43.910
		298.02	nM	-1.800
		93.13	nM	-4.150
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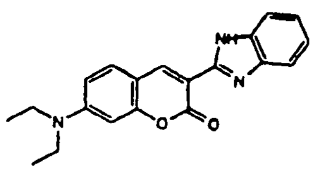
		9.09	nM	-31.110
		2.84	nM	-26.760
		0.80	nM	-28.270
 59-0122	333.39			
		100.00	uM	-19.050
		31.25	uM	-12.080
		9.77	uM	-7.610
		3.05	uM	25.210
		953.67	nM	83.580
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		93.13	nM	63.890
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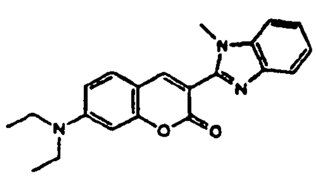
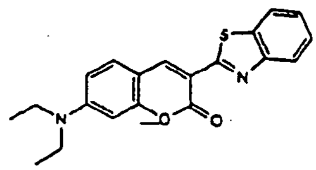
		9.09	nM	45.320
		2.84	nM	37.780
		0.80	nM	27.030
 59-0123	347.42			
		100.00	uM	34.430
		31.25	uM	34.710
		9.77	uM	38.620
		3.05	uM	55.100
		953.67	nM	51.900
		298.02	nM	41.410
		93.13	nM	29.970
		29.10	nM	13.760
		9.09	nM	17.120
		2.84	nM	13.480
		0.80	nM	1.190



59-0124	350.44			
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		31.25	uM	81.500
		9.77	uM	145.880
		3.05	uM	135.830
		953.67	nM	268.990
		298.02	nM	224.290
		93.13	nM	134.850
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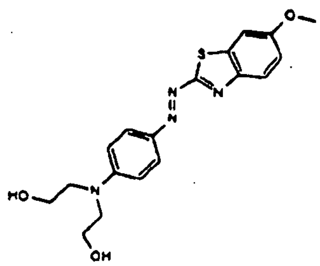
		9.09	nM	80.390
		2.84	nM	63.060
		0.80	nM	51.460



59-0125	372.45			
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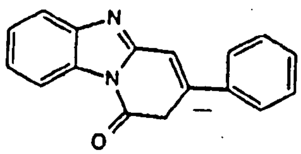
		31.25	uM	67.530
		9.77	uM	54.120
		3.05	uM	28.700
		953.67	nM	21.580
		298.02	nM	22.280
		93.13	nM	22.700
		29.10	nM	1.630
		9.09	nM	15.700
		2.84	nM	9.840
		0.80	nM	8.460



59-0126	260.30				
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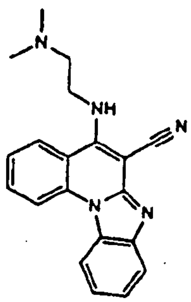
		31.25	uM	-13.100	
		9.77	uM	9.270	
		3.05	uM	40.530	
		953.67	nM	21.390	
		298.02	nM	25.660	
		93.13	nM	9.430	
		29.10	nM	6.360	
		9.09	nM	6.510	
		2.84	nM	0.060	
		0.80	nM	3.750	



59-0127	329.41				
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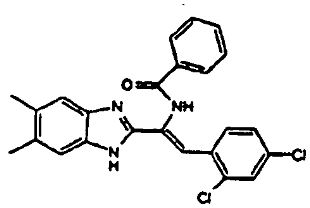
		31.25	uM	-21.820	
		9.77	uM	-6.060	
		3.05	uM	-3.900	
		953.67	nM	-8.820	
		298.02	nM	-6.200	
		93.13	nM	11.880	
		29.10	nM	1.610	
		9.09	nM	3.600	
		2.84	nM	-2.070	
		0.80	nM	4.220	



59-0128	436.34				
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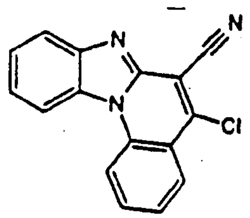
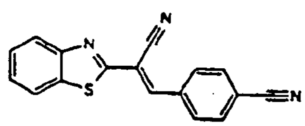
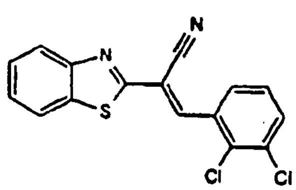
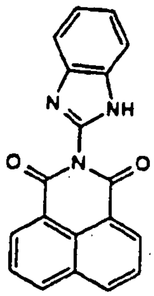
		31.25	uM		
		9.77	uM		
		3.05	uM		
		953.67	nM		
		298.02	nM		
		93.13	nM		
		29.10	nM		

		[illegible]	nM			
		2.84	nM			
		0.80	nM			
 59-0129	277.71					
		100.00	uM	-20.48		
		31.25	uM	-21.21		
		9.77	uM	44.36		
		3.05	uM	4.38		
		953.67	nM	5.9		
		298.02	nM	3.6		
		93.13	nM	2.07		
		29.10	nM	4.22		
		9.09	nM	-0.68		
		2.84	nM	12.48		
		0.80	nM	-0.53		
 59-0130	287.34					
		100.00	uM	4.38		
		31.25	uM	8.35		
		9.77	uM	5.91		
		3.05	uM	4.98		
		953.67	nM	0.39		
		298.02	nM	8.66		
		93.13	nM	2.85		
		29.10	nM	3.6		
		9.09	nM	4.36		
		2.84	nM	8.96		
		0.80	nM	24.75		
 59-0131	331.22					
		100.00	uM	8.75		
		31.25	uM	0.12		
		9.77	uM	-10.38		
		3.05	uM	-6.39		
		953.67	nM	-2.81		
		298.02	nM	1.61		
		93.13	nM	-1.98		
		29.10	nM	-2.59		
		9.09	nM	0.14		
		2.84	nM	-5.77		

		0.80	nM	-0.5	
 59-0132	313.32				
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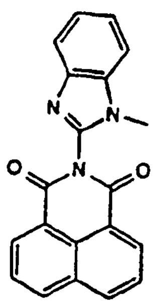
		9.77	uM	-14.37	
		3.05	uM	-12.92	
		953.67	nM	-13.54	
		298.02	nM	-10.38	
		93.13	nM	-3.65	
		29.10	nM	-7.66	
		9.09	nM	-6.18	
		2.84	nM	-9.97	
		0.80	nM	-2.81	
 59-0133	327.34				
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		31.25	uM	-16.91	
		9.77	uM	-17.31	
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		953.67	nM	-9.34	
		298.02	nM	-12.69	
		93.13	nM	-11.23	
		29.10	nM	-17.74	
		9.09	nM	6.02	
		2.84	nM	-4.71	
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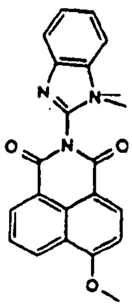 59-0134		357.37				
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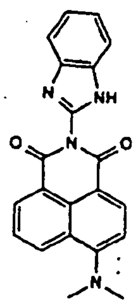
			9.77	uM		
			3.05	uM		
			953.67	nM		
			298.02	nM		
			93.13	nM		
			29.10	nM		
			9.09	nM		
			2.84	nM		
			0.80	nM		
 59-0135		356.39				
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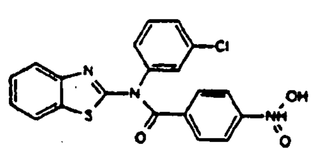
			3.05	uM	0.97	
			953.67	nM	11.68	
			298.02	nM	-1.13	
			93.13	nM	-1.55	
			29.10	nM	-2.81	
			9.09	nM	12.11	
			2.84	nM	-5.75	
			0.80	nM	4.54	
 59-0136		411.87				
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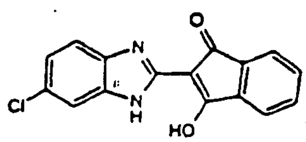
			31.25	uM		
			9.77	uM		
			3.05	uM		
			953.67	nM		

		298.02	nM	
		93.13	nM	
		29.10	nM	
		9.09	nM	
		2.84	nM	
		0.80	nM	
 59-0137	296.71			
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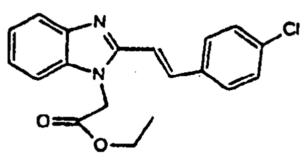
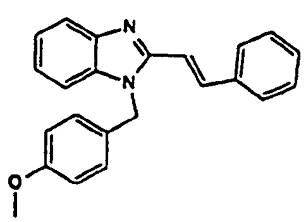
		31.25	uM	
		9.77	uM	
		3.05	uM	
		953.67	nM	
		298.02	nM	
		93.13	nM	
		29.10	nM	
		9.09	nM	
		2.84	nM	
		0.80	nM	
 59-0138	340.81			
		100.00	uM	-6.91
		31.25	uM	-12.68
		9.77	uM	4.59
		3.05	uM	32.61
		953.67	nM	19.07
		298.02	nM	8.18
		93.13	nM	2.26
		29.10	nM	12.22
		9.09	nM	56.42
		2.84	nM	7.24
		0.80	nM	1.63
 59-0139	340.43			
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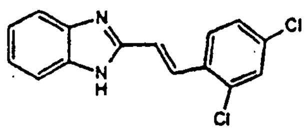
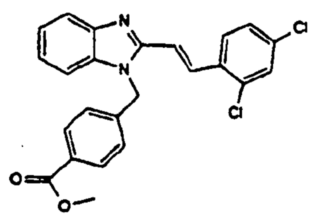
		31.25	uM	44.59
		9.77	uM	53.62
		3.05	uM	30.42
		953.67	nM	28.25
		298.02	nM	20.31
		93.13	nM	18.6

		[illegible] 29.10	nM	[illegible]	
		9.09	nM	13.93	
		2.84	nM	18.61	
		0.80	nM	10.05	
 59-0140	289.17				
		100.00	uM		
		31.25	uM		
		9.77	uM		
		3.05	uM		
		953.67	nM		
		298.02	nM		
		93.13	nM		
		29.10	nM		
		9.09	nM		
		2.84	nM		
		0.80	nM		
 59-0141	437.33				
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		31.25	uM	5.69	
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		3.05	uM	43.96	
		953.67	nM	44.73	
		298.02	nM	37.12	
		93.13	nM	24.36	
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		9.09	nM	26.71	
		2.84	nM	15.96	
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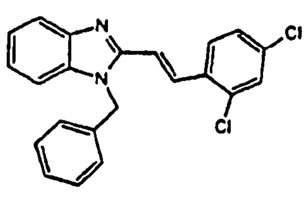 59-0142	379.29				
		100.00	uM	9.43	
		31.25	uM	33.72	
		9.77	uM	47.33	
		3.05	uM	40.19	
		953.67	nM	36.53	
		298.02	nM	29.94	
		93.13	nM	22.11	

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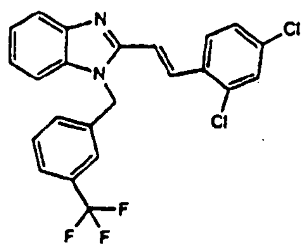
		9.09	nM	19.14
		2.84	nM	10.38
		0.80	nM	17 12
 59-0143	447.29			
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		953.67	nM	36.94
		298.02	nM	27.23
		93.13	nM	16.99
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		9.09	nM	14.42
		2.84	nM	11.33
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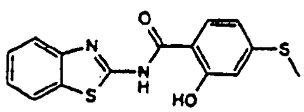 59-0144	316.40			
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		3.05	uM	53.89
		953.67	nM	43.11
		298.02	nM	29.2
		93.13	nM	18.5
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		9.09	nM	5.54
		2.84	nM	3.71
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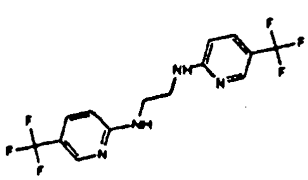 59-0145	350.27			
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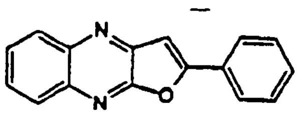
		9.77	uM	446.93
		3.05	uM	434.17
		953.67	nM	238.34
		298.02	nM	45.99
		93.13	nM	9.22
		29.10	nM	7.71
		9.09	nM	0.11

		2.84	nM	6.27
		0.80	nM	3.55
 59-0146	246.27			
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		3.05	uM	-16.45
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		93.13	nM	-50.13
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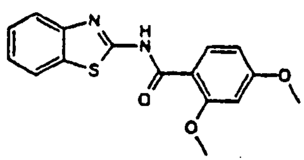 59-0147	314.36			
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		9.77	uM	-60.29
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		93.13	nM	323.59
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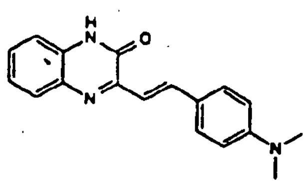 59-0148	291.35			
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		953.67	nM	-2.42
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		93.13	nM	-30.87
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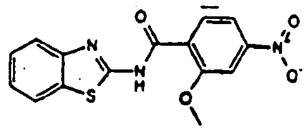 59-0149	329.33					
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		298.02	nM	163.5		
		93.13	nM	223.57		
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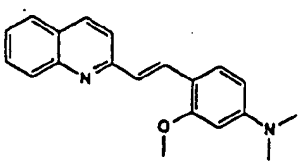 59-0150	304.39					
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		9.77	uM	419.26		
		3.05	uM	497.21		
		953.67	nM	295.19		
		298.02	nM	193.35		
		93.13	nM	99.48		
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		9.09	nM	59		
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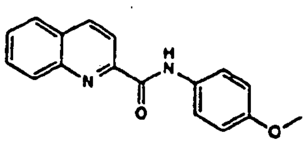 59-0151	278.311					
59-0151		100.00	uM	-6.660		
		31.25	uM	18.240		
		9.77	uM	18.300		
		3.05	uM	11.690		
		953.67	nM	8.500		
		298.02	nM	9.070		
		93.13	nM	6.110		
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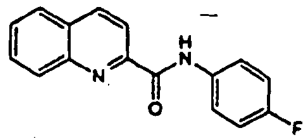
		9.09	nM	7.700		
		2.84	nM	2.000		
		0.80	nM	1.210		

 59-0152	266.275					
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		3.05	uM	12.620		
		953.67	nM	7.350		
		298.02	nM	4.290		
		93.13	nM	9.750		
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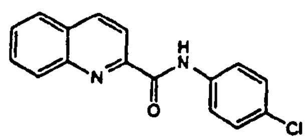 59-0153	282.73					
59-0153		100.00	uM	-4.150		
		31.25	uM	-0.390		
		9.77	uM	11.120		
		3.05	uM	14.840		
		953.67	nM	9.520		
		298.02	nM	11.570		
		93.13	nM	-0.160		
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		9.09	nM	-0.960		
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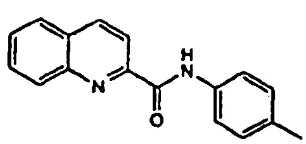 59-0154	262.312					
59-0154		100.00	uM	0.290		
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		9.77	uM	15.680		
		3.05	uM	14.540		
		953.67	nM	13.170		
		298.02	nM	5.540		
		93.13	nM	2.690		
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		9.09	nM	2.460		
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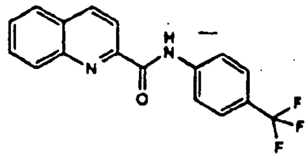 59-0155	316.282			
59-0155		100.00	uM	-2.950
		31.25	uM	1.900
		9.77	uM	-9.450
		3.05	uM	-0.220
		953.67	nM	0.690
		298.02	nM	5.090
		93.13	nM	-3.250
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		9.09	nM	-1.900
		2.84	nM	9.480
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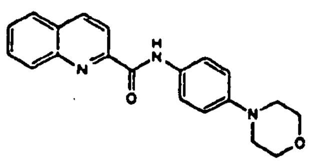 59-0156	333.391			
59-0156		100.00	uM	5.840
		31.25	uM	2.050
		9.77	uM	7.960
		3.05	uM	6.890
		953.67	nM	-0.370
		298.02	nM	-1.880
		93.13	nM	-3.550
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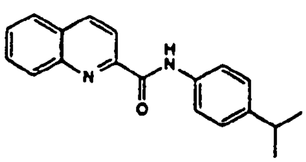
		9.09	nM	-1.590
		2.84	nM	2.650
		0.80	nM	2.500
 59-0157	290.366			
59-0157		100.00	uM	-6.440
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		9.77	uM	19.930
		3.05	uM	11.440
		953.67	nM	8.570
		298.02	nM	-7.190
		93.13	nM	0.080
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		9.09	nM	-4.460
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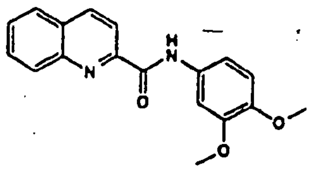
		0.80	nM	9.920



59-0158	308.337					
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		9.77	uM		16.140	
		3.05	uM		27.060	
		953.67	nM		9.930	
		298.02	nM		11.900	
		93.13	nM		2.810	
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		9.09	nM		0.690	
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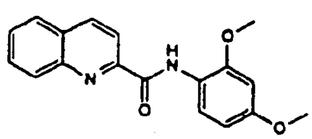

59-0159	308.337					
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		9.77	uM		4.700	
		3.05	uM		10.910	
		953.67	nM		2.800	
		298.02	nM		9.710	
		93.13	nM		4.830	
		29.10	nM		0.650	
		9.09	nM		5.900	
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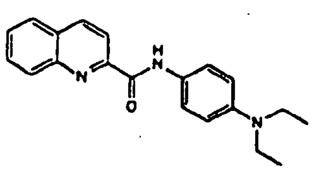
		0.80	nM		6.250	



59-0160	319.408					
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		9.77	uM		5.300	
		3.05	uM		15.910	
		953.67	nM		6.610	
		298.02	nM		11.380	
		93.13	nM		4.460	
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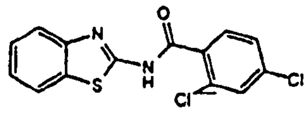
		9.09	nM		4.700	
		2.84	nM		-0.650	
		0.80	nM		7.560	

 59-0196	323.201						
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		9.77	uM				
		3.05	uM				
		953.67	nM				
		298.02	nM				
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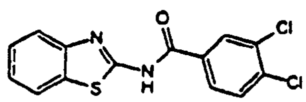
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				
 59-0197	323.201						
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		3.05	uM				
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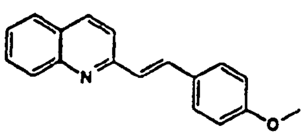
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				
 59-0198	261.324						
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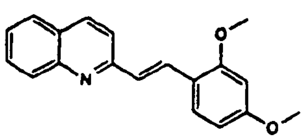
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				
 59-0199	291.35						
59-0199		100.00	uM				
		31.25	uM				

		[illegible]	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
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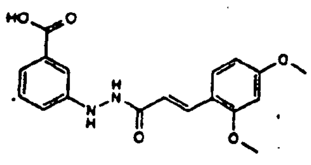 59-0200	342.351					
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		953.67	nM			
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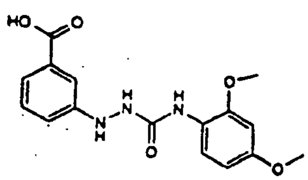
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
 59-0201	331.328					
59-0201		100.00	uM			
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		29.10	nM			
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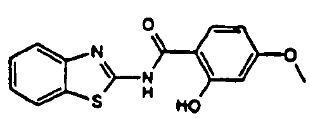
		2.84	nM			
		0.80	nM			
 59-0202	300.336					
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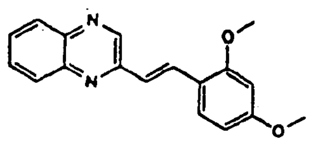
		93.13	nM			
		[illegible]9.10	nM			

		9.09	nM			
		2.84	nM			
		0.80	nM			
 59-0203	292.338					
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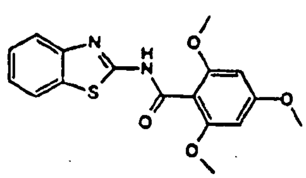 59-0204	344.389					
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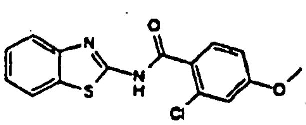
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
 59-0205	318.782					
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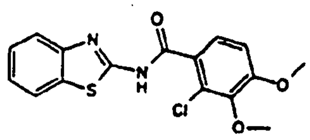
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			

 59-0206	348.808						
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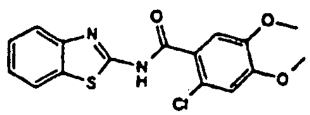
		2.84	nM				
		0.80	nM				
 59-0207	348.808						
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		9.09	nM				
		2.84	nM				
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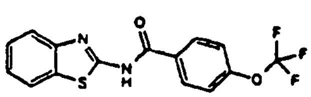 59-0208	338.307						
59-0208		100.00	uM				
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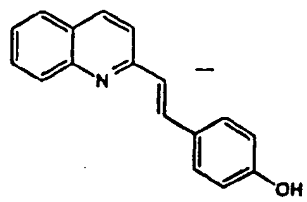
		3.05	uM				
		953.67	nM				
		298.02	nM				
		93.13	nM				
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				

 59-0209	247.297						
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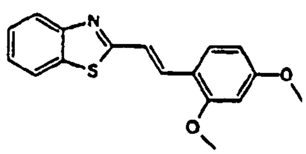
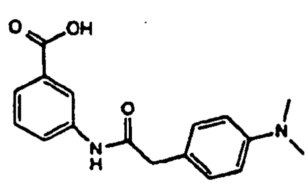
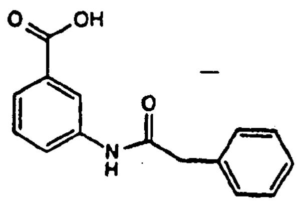
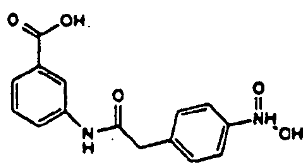
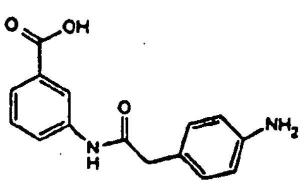
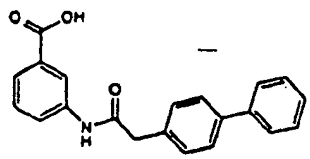
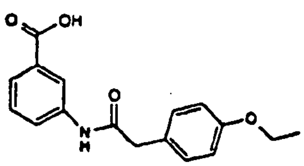
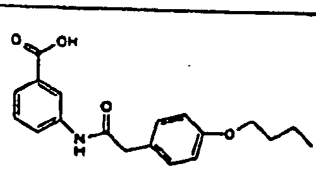
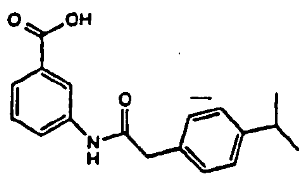
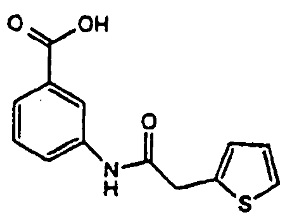
		93.13	nM				
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				
 59-0210	297.376						
59-0210		100.00	uM				
		31.25	uM				
		9.77	uM				
		3.05	uM				
		953.67	nM				
		298.02	nM				
		93.13	nM				
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				
 59-8000	298.342						
59-8000		100.00	uM				
		31.25	uM				
		9.77	uM				
		3.05	uM				
		953.67	nM				
		298.02	nM				
		93.13	nM				
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				

 59-8001	255.273					
59-8001		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
 59-8002	302.286					
59-8002		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
 59-8003	270.288					
59-8003		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			

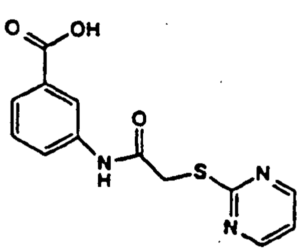
 59-8004	331.371					
59-8004		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
 59-8005	299.326					
59-8005		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
 59-8006	327.38					
59-8006		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			



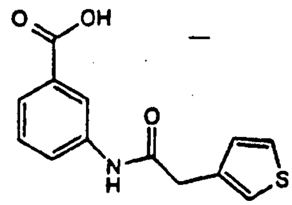
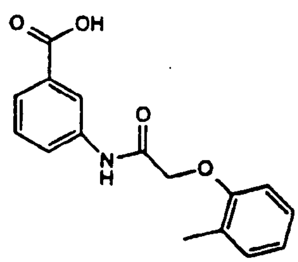
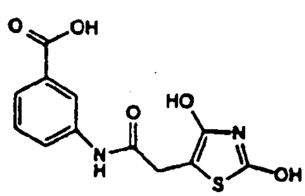
59-8007	297.354						
59-8007		100.00	uM				
		31.25	uM				
		9.77	uM				
		3.05	uM				
		953.67	nM				
		298.02	nM				
		93.13	nM				
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				

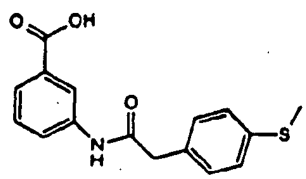
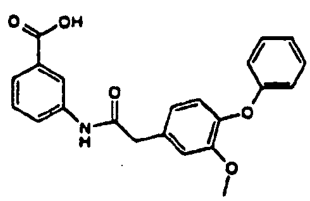
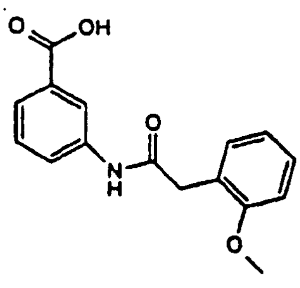


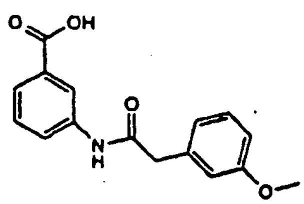
59-8008	261.299						
59-8008		100.00	uM				
		31.25	uM				
		9.77	uM				
		3.05	uM				
		953.67	nM				
		298.02	nM				
		93.13	nM				
		29.10	nM				
		9.09	nM				
		2.84	nM				
		0.80	nM				



59-8009	289.313						
59-8009		100.00	uM				
		31.25	uM				
		9.77	uM				
		3.05	uM				
		953.67	nM				
		298.02	nM				
		93.13	nM				
		29.10	nM				
		9.09	nM				

		[illegible]	nM			
		0.80	nM			
 59-8010	281.299					
59-8010		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
 59-8011	285.299					
59-8011		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
 59-8012	294.285					
59-8012		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			

		[illegible]	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
 59-8013	301.364					
59-8013		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
 59-8014	377.396					
59-8014		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
 59-8015	285.299					
59-8015		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			

		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			
 59-6016	285.299					
59-6016		100.00	uM			
		31.25	uM			
		9.77	uM			
		3.05	uM			
		953.67	nM			
		298.02	nM			
		93.13	nM			
		29.10	nM			
		9.09	nM			
		2.84	nM			
		0.80	nM			

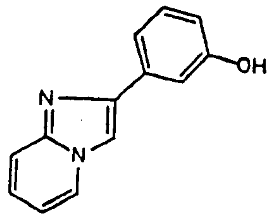
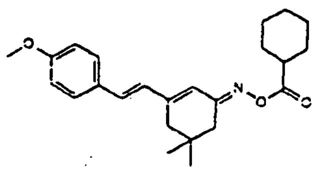
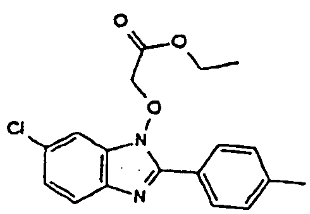
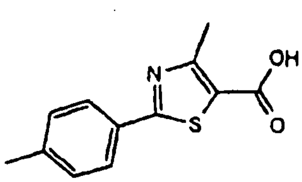
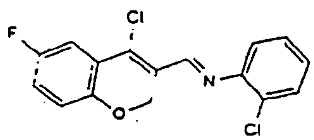
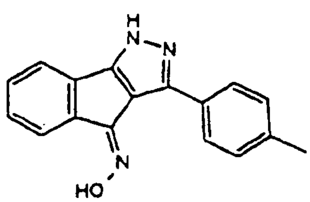
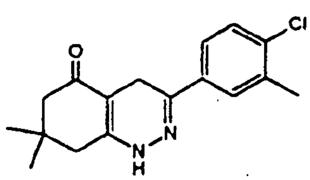
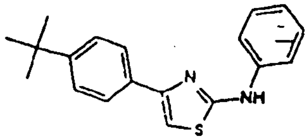
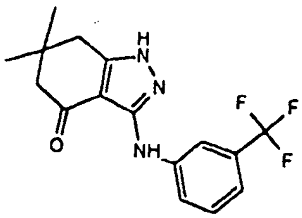
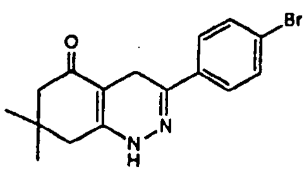
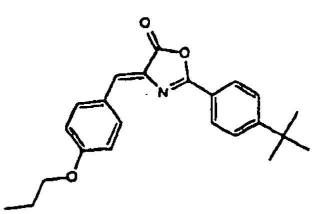
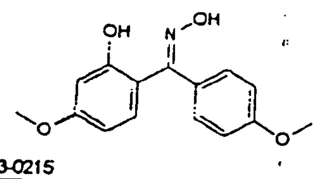
CHEMISTRY	Concentration		ABA-S
 51-2229			
51-2229	100.00	uM	125.320
	10.00		28.260
210.236	2.00		20.140
	0.40		-9.740
	0.08		-9.710
 92-3052			
92-3052	131.056	uM	-9.28
	13.106		113.80
381.516	2.621		12.61
	0.524		20.25
	0.105		24.45
 92-3390			
92-3390	145.012	uM	-8.05
	14.501		31.57
344.798	2.900		139.66
	0.580		49.62
	0.116		21.01
 92-3552			
92-3552	214.326	uM	108.15

Figure 4

	21.433		69.74
233.289	4.287		31.59
	0.857		39.70
	0.171		18.29
 92-6353			
92-6353	155.199	uM	
	31.040		204.14
322.166	15.520		154.94
	3.104		28.09
	1.552		
	0.310		3.53
 92-8007			
92-8007	181.613	uM	-16.65
	36.323		58.65
275.311	18.161		142.33
	3.632		45.65
	1.816		
	0.363		4.47
 92-8215			
92-8215	165.123	uM	32.90
	33.025		151.08
302.805	16.512		132.29
	3.302		59.90
	1.651		
	0.330		23.34

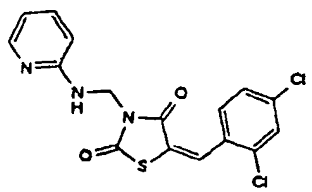
 92-8258			
92-8258	162.102	uM	-16.65
	32.420		157.44
308.447	16.210		101.04
	3.242		39.02
	1.621		
	0.324		12.78
 92-8362			
92-8362	154.647	uM	136.79
	30.929		137.00
323.318	15.465		65.02
	3.093		17.34
	1.546		
	0.309		0.41
 92-8372			
92-8372	150.045	uM	63.76
	30.009		134.71
333.234	15.004		92.08
	3.001		31.35
	1.500		
	0.300		13.20
 92-9183			

92-9183			
	137.568	uM	-22.80
-	13.757		16.61
363.457	2.751		101.96
	1.376		
	0.550		58.17
	0.110		38.47



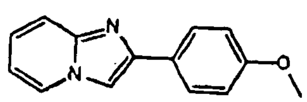
93-0215

93-0215			
	182.957	uM	115.230
	18.296		88.110
273.288	3.659		20.870
	0.732		-28.680
	0.146		5.250



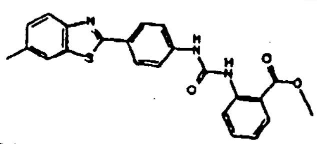
93-0399

93-0399			
	131.491	uM	128.130
	13.149		38.560
380.253	2.630		41.240
	0.526		-4.910
	0.105		3.910



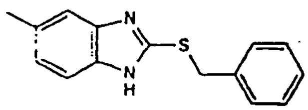
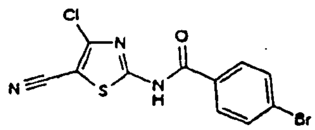
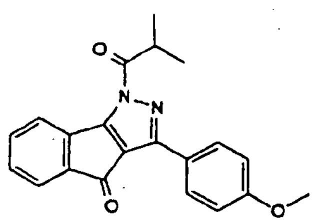
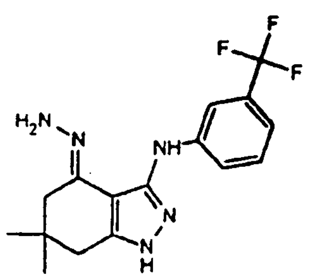
93-0587

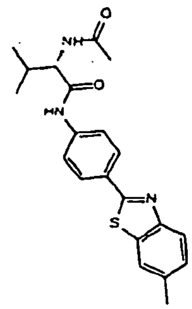
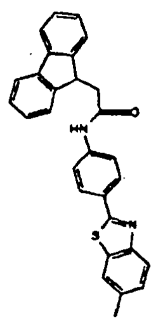
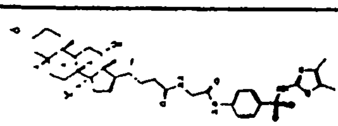
93-0587			
	222.953	uM	178.130
	22.295		60.410
224.263	4.459		-0.180
	0.892		-3.470
	0.178		-8.490

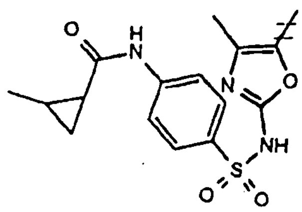


93-1327

93-1327			
	119.764	uM	-42.000
	11.976		119.130
417.487	2.395		67.930
	0.479		8.520

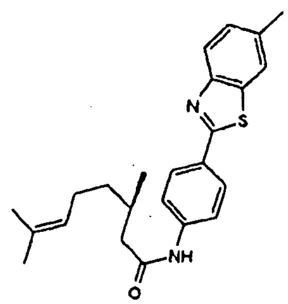
	0.096		14.870
 93-1340			
93-1340	196.576	uM	-31.290
	19.658		127.340
254.355	3.932		35.710
	0.786		37.630
	0.157		7.280
 93-1474			
93-1474	145.940	uM	-45.110
	14.594		110.290
342.607	2.919		35.080
	0.584		109.040
	0.117		40.130
 93-1766			
93-1766	144.348	uM	
	14.435		
346.386	2.887		
	0.577		
	0.115		
 93-1866			
93-1866	148.214	uM	75.940
	14.821		173.150

337.349	2.964			2.600
--	0.593			-7.360
	0.119			-25.160
 850-7377				
850-7377	131.062	uM		-50.32
	13.106			68.27
381.486	2.621			116.61
	0.524			61.26
	0.105			35.86
 850-7413				
850-7413	111.964	uM		-40.44
	11.196			-2.55
446.572	2.239			157.01
	0.448			78.73
	0.090			23.91
 850-7449				
850-7449	69.936	uM		-42.42
	6.994			73.79
714.923	1.399			112.16
	0.280			75.24
	0.056			26.38



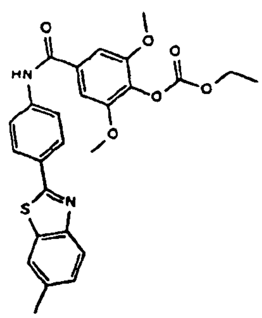
850-7485

850-7485	143.099	uM	-42.91
	14.310		28.36
349.409	2.862		153.04
	0.572		74.27
	0.114		50.28



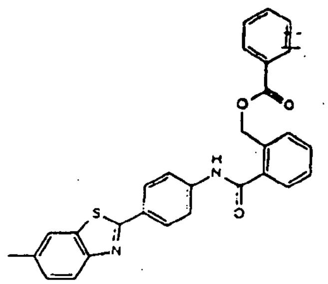
850-7991

850-7991	127.367	uM	-16.87
	12.737		8.95
392.565	2.547		105.51
	0.509		47.53
	0.102		54.26



850-8170

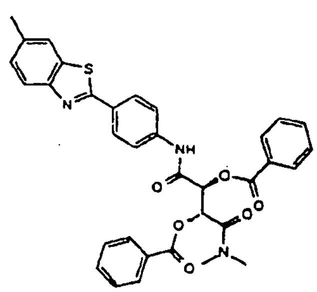
850-8170	101.513	uM	-33.79
	10.151		158.65
492.55	2.030		126.27
	0.406		43.05
	0.081		50.00



850-8205

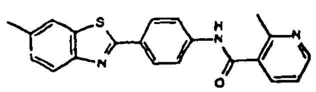
850-8205		104.478	uM	-39.52
		10.448		51.18
	478.57	2.090		163.82
		0.418		106.06
		0.084		73.68

CHIRAL



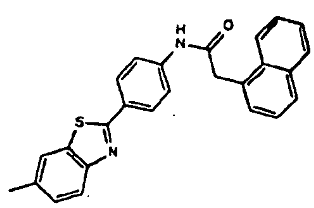
850-8241

850-8241		82.279	uM	-2.07
		8.228		181.77
	607.686	1.646		118.23
		0.329		66.73
		0.066		36.14



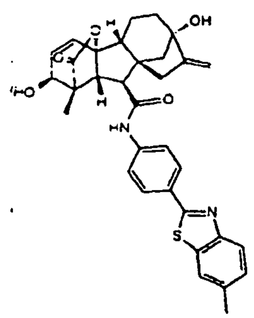
850-8278

850-8278		139.101	uM	-40.09
		13.910		39.00
	369.451	2.782		182.38
		0.556		122.84
		0.111		78.90



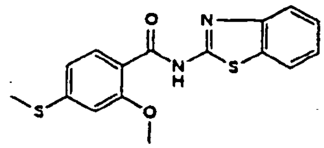
850-8387

850-8387	122.392	uM	-17.06
	12.239		130.31
408.523	2.448		129.75
	0.490		62.69
	0.098		40.74



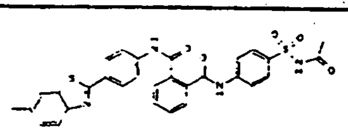
850-8459

850-8459	87.921	uM	-21.13
	8.792		11.30
568.692	1.758		131.92
	0.352		71.13
	0.070		58.55



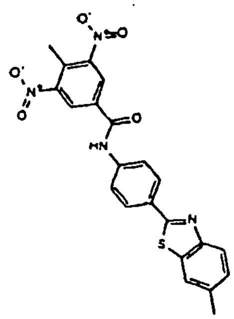
850-8613

850-8613	151.319	uM	-28.05
	15.132		86.56
330.428	3.026		381.37
	0.605		256.32
	0.121		122.93



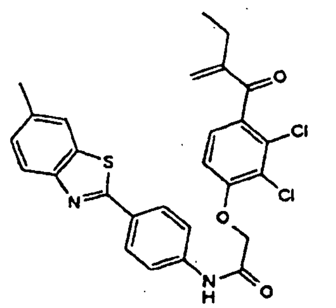
850-8637

850-8637	85.518	uM	-25.17
	8.552		33.36
584.673	1.710		122.49
	0.342		57.19
	0.068		37.42



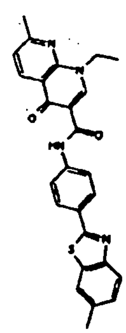
850-8889

850-8889	111.493	uM	-17.470
	11.149		142.970
448.457	2.230		74.150
	0.446		21.010
	0.089		8.530



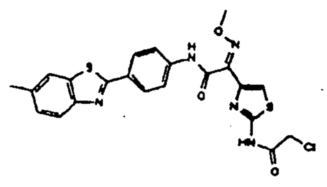
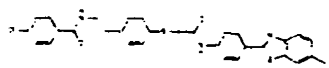
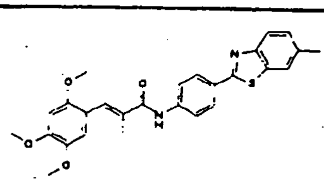
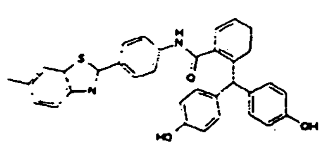
850-8964

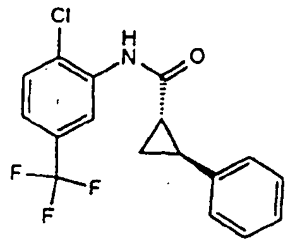
850-8964	95.156	uM	-30.92
	9.516		44.99
525.454	1.903		126.29
	0.381		49.84
	0.076		44.99



850-9071

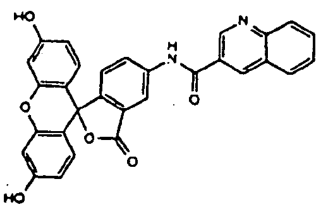
850-9071	109.998	uM	-24.620
	11.000		84.120
454.552	2.200		149.030
	0.440		54.540

		0.088		23.540
 850-9106				
850-9106		100.000	uM	-15.710
		10.000		99.820
	499.999	2.000		111.960
		0.400		74.500
		0.080		23.150
 850-9142				
850-9142		85.596	uM	-14.980
		8.560		165.770
	584.138	1.712		66.650
		0.342		27.780
		0.068		0.670
 850-9179				
850-9179		105.367	uM	-24.630
		10.536		105.200
	474.579	2.107		89.280
		0.421		46.110
		0.084		19.160
 850-9212				
850-9212		92.139	uM	-26.580
		9.214		40.900
	542.657	1.843		111.690
		0.369		76.950
		0.074		30.840



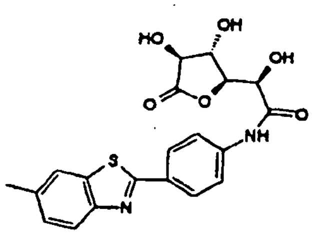
850-9287

850-9287	147.170	uM	-15.82
	14.717		15.82
339.744	2.943		130.71
	0.589		91.11
	0.118		69.05



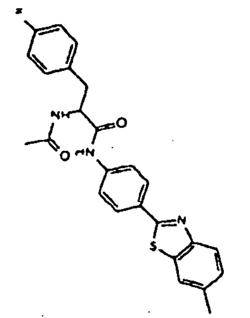
850-9356

850-9356	99.506	uM	-24.650
	9.951		83.140
502.482	1.990		168.810
	0.398		45.470
	0.080		9.740



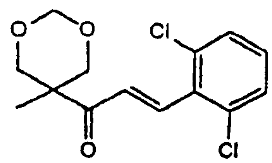
850-9467

850-9467	120.646	uM	-19.800
	12.065		112.990
414.436	2.413		122.730
	0.483		43.520
	0.097		33.140



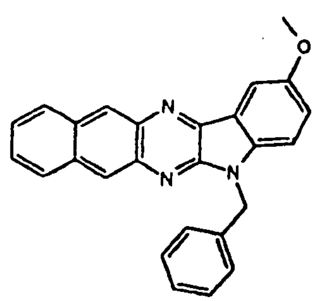
850-9576

850-9576		111.724	uM	-27.430
		11.172		90.560
	447.532	2.234		101.610
		0.447		44.900
		0.089		19.930



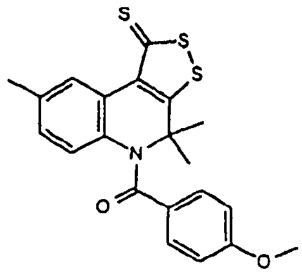
895-0262

895-0262		166.019	uM	-19.18
		33.204		-12.60
	301.169	16.602		148.28
		3.320		-2.23
		0.332		-3.07



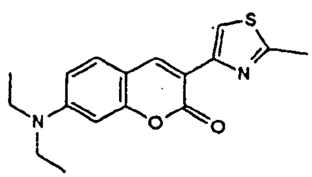
895-0268

895-0268		128.383	uM	-18.87
		25.677		40.25
	389.458	12.838		169.96
		2.568		195.29
		0.257		14.02



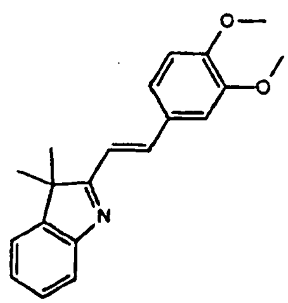
895-0594

895-0594		120.896	uM	-21.63
		12.090		25.89
	413.58	2.418		122.10
		0.484		75.32
		0.097		39.42



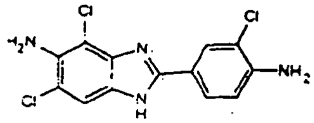
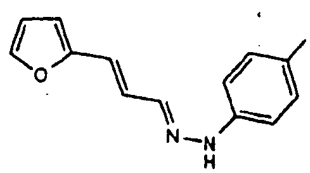
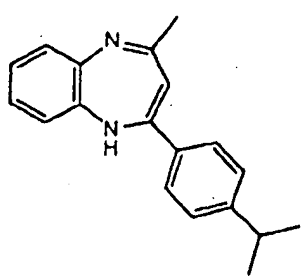
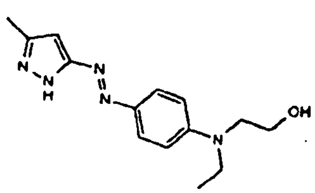
895-0857

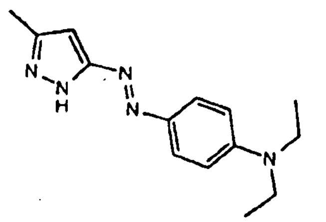
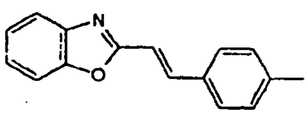
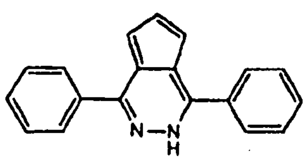
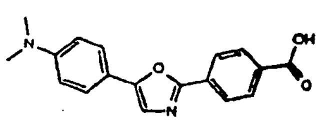
895-0857		159.028	uM	-30.48
		15.903		148.74
	314.407	3.181		74.54
		0.636		25.82
		0.127		3.66

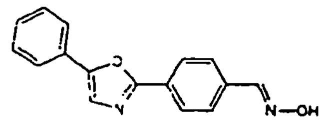
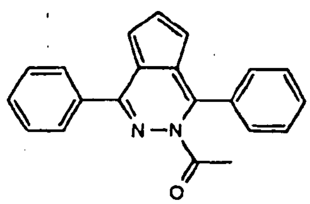
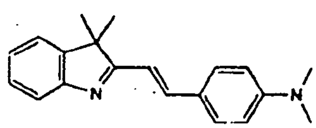
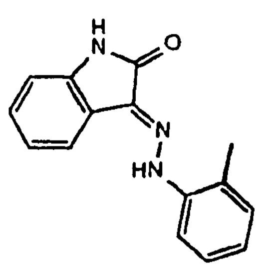


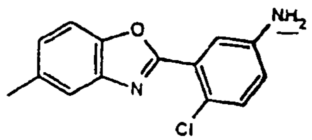
895-0984

895-0984		162.655	uM	-31.08
		16.265		325.06
	307.393	3.253		87.51
		0.651		40.39
		0.130		16.03

 895-1161			
895-1161	152.625	uM	-5.51
	15.263		109.31
327.602	3.053		56.06
	0.611		29.49
	0.122		24.71
 895-1420			
895-1420	220.965	uM	-19.47
	22.097		110.90
226.279	4.419		49.94
	0.884		33.65
	0.177		20.06
 895-1679			
895-1679	180.910	uM	-30.36
	18.091		111.72
276.383	3.618		102.83
	0.724		18.01
	0.145		0.44
 895-1691			
895-1691	182.922	uM	-16.29
	18.292		50.84
273.34	3.658		105.70

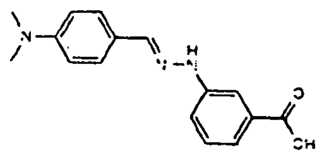
	0.732		60.23
	0.146		23.42
 895-1754			
895-1754	194.295	uM	-31.44
	19.430		132.78
257.341	3.886		75.39
	0.777		39.30
	0.155		16.19
 895-1888			
895-1888	212.504	uM	-33.65
	21.250		29.75
235.286	4.250		148.84
	0.850		73.77
	0.170		28.14
 895-2474			
895-2474	184.952	uM	-20.74
	18.495		128.69
270.335	3.699		68.37
	0.740		43.27
	0.148		19.44
 895-2475			
895-2475	162.159	uM	265.41
	16.216		287.86
308.337	3.243		227.34
	0.649		65.40
	0.130		28.96

 895-2544				
895-2544		189.186	uM	17.53
		18.919		136.50
	264.284	3.784		59.15
		0.757		24.75
		0.151		11.86
 895-3113				
895-3113		160.067	uM	-22.22
		16.007		224.52
	312.372	3.201		68.48
		0.640		43.36
		0.128		30.56
 895-3306				
895-3306		172.170	uM	-23.24
		17.217		38.63
	290.41	3.443		333.10
		0.689		164.63
		0.138		64.33
 895-3810				
895-3810		198.973	uM	89.79
		19.897		106.75
	251.289	3.979		73.78
		0.796		33.45
		0.159		16.86



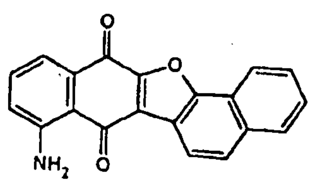
895-3846

895-3846	193.267	uM	-21.41
	19.327		13.40
258.708	3.865		114.46
	0.773		52.12
	0.155		38.29



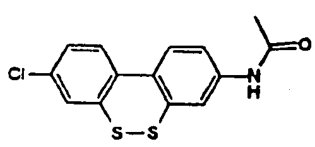
895-4642

895-4642	176.473	uM	6.97
	17.647		283.99
283.331	3.529		447.51
	0.706		304.86
	0.141		100.45



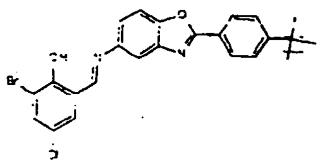
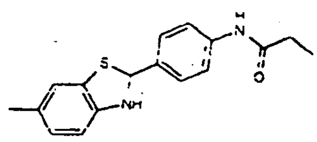
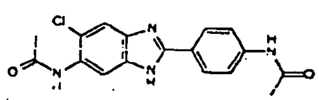
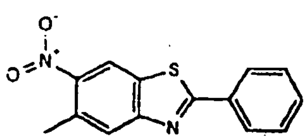
895-4843

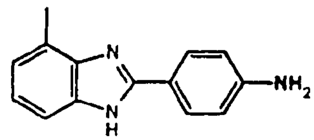
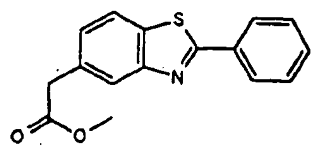
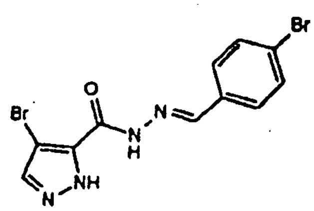
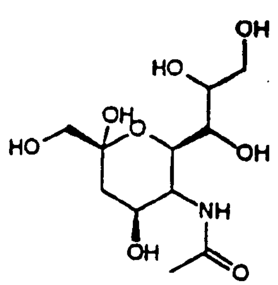
895-4843	159.581	uM	-17.18
	15.958		24.54
313.312	3.192		100.12
	0.638		60.37
	0.128		27.85

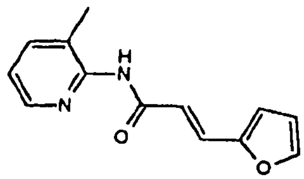
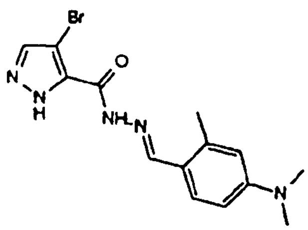
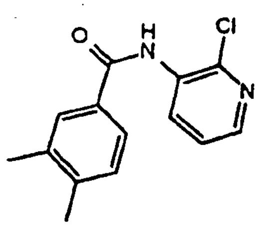


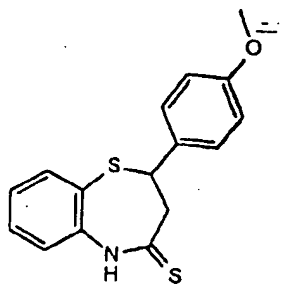
895-5185

895-5185	162.433	uM	-6.47
	16.243		213.42
307.821	3.249		107.83
	0.650		46.75
	0.130		18.27

 895-5960			
895-5960	103.348	uM	-10.03
	10.335		158.04
483.798	2.067		62.07
	0.413		34.47
	0.083		7.24
 895-6353			
895-6353	167.565	uM	-10.45
	16.755		21.59
298.408	3.351		101.77
	0.670		54.91
	0.134		24.15
 895-6643			
895-6643	145.862	uM	100.09
	14.586		74.25
342.786	2.917		16.86
	0.583		-0.89
	0.117		-7.94
 895-7828			
895-7828	184.973	uM	-32.44
	18.497		-29.24
270.31	3.699		86.15
	0.740		125.64
	0.148		-30.80

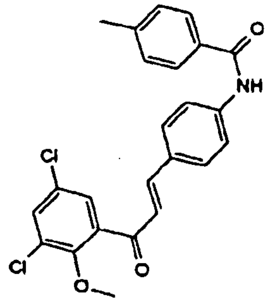
 895-7985				
895-7985		223.935	uM	122.070
		22.394		3.900
	223.279	4.479		-7.790
		0.898		5.520
		0.179		-2.270
 895-7997				
895-7997		176.461	uM	
		17.646		
	283.349	3.529		
		0.706		
		0.141		
 895-8053				
895-8053		134.398	uM	
		13.440		
	372.03	2.688		
		0.538		
		0.108		
 895-8137				
895-8137		169.326	uM	

		16.933		
	295.288	3.387		
		0.677		
		0.135		
 895-8185				
895-8185		219.057	uM	
		21.906		
	228.251	4.381		
		0.876		
		0.175		
 895-8286				142.210
895-8286		142.785	uM	40.380
		14.277		17.850
	350.225	2.855		-10.890
		0.571		6.580
		0.114		
 895-8383				
895-8383		191.774	uM	-44.020
		19.177		76.460
	260.724	3.835		135.940
		0.767		77.030
		0.153		37.630



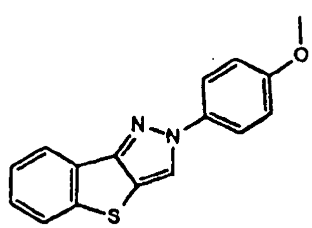
895-8862

895-8862		165.876	uM	54.72
		16.588		159.21
	301.43	3.318		113.97
		0.664		41.96
		0.133		38.28



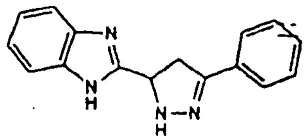
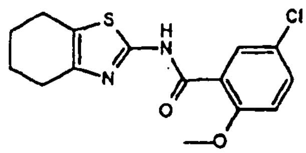
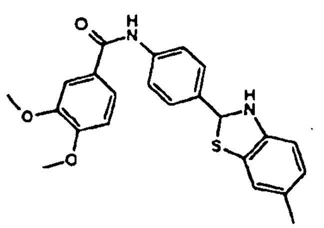
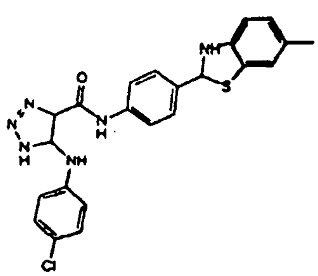
895-9683

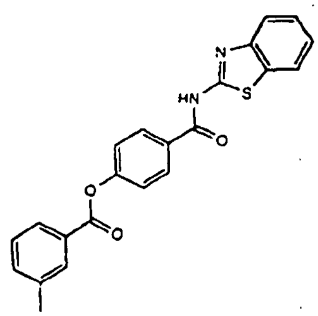
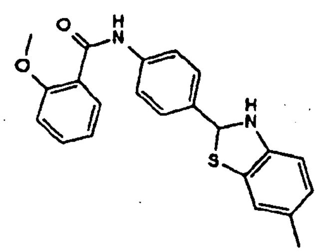
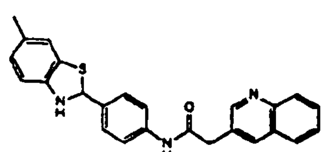
895-9683		113.552	uM	-20.67
		11.355		201.56
	440.326	2.271		12.55
		0.454		0.62
		0.091		-0.69

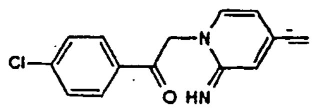


895-9898

895-9898		178.349	uM	-29.16
		17.835		0.62
	280.349	3.567		182.84
		0.713		118.56
		0.143		42.75

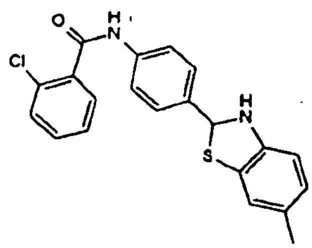
 896-0122			
896-0122	190.610	uM	-14.15
	19.061		151.42
262.316	3.812		56.90
	0.762		19.20
	0.152		11.42
 896-0246			
896-0246	154.888	uM	-17.57
	15.489		34.35
322.814	3.098		102.03
	0.620		46.52
	0.124		20.52
 896-0255			
896-0255	123.000	uM	-17.14
	12.300		67.75
406.504	2.460		168.78
	0.492		61.27
	0.098		49.97
 896-0345			
896-0345	107.532	uM	-18.86
	10.753		77.80

464.979	2.151		188.94
	0.430		106.12
	0.086		37.18
 896-0390			
896-0390	128.718	uM	-16.90
	12.872		87.23
388.445	2.574		210.25
	0.515		73.36
	0.103		28.25
 896-0535			
896-0535	132.810	uM	-10.41
	13.281		73.84
376.478	2.656		199.80
	0.531		102.12
	0.106		35.72
 896-0554			
896-0554	121.499	uM	-16.32
	12.150		105.46
411.527	2.430		115.43
	0.486		53.88
	0.097		27.03



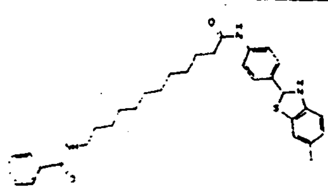
896-0686

896-0686		191.774	uM	-19.80
		19.177		176.04
	260.724	3.836		115.02
		0.767		97.67
		0.153		25.27



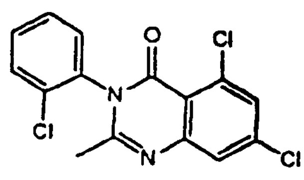
896-0692

896-0692		131.269	uM	22.78
		13.127		149.23
	380.897	2.625		78.33
		0.525		51.08
		0.105		46.12



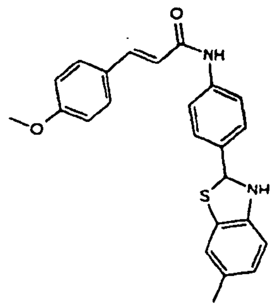
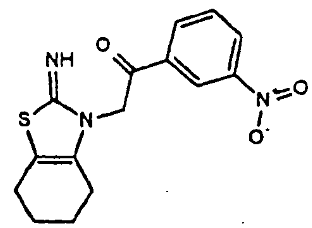
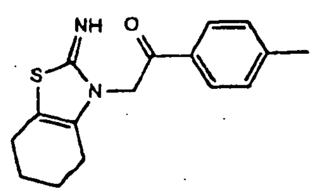
896-0719

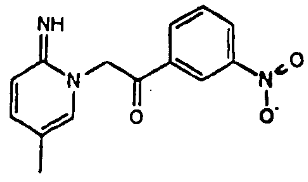
896-0719		91.950	uM	-6.49
		9.195		187.43
	543.774	1.839		127.43
		0.368		50.04
		0.074		36.16



898-0773

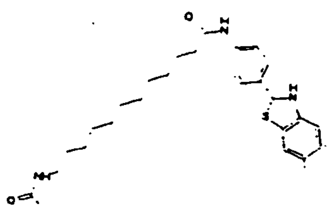
898-0773		147.228	uM	-13.94
		14.723		175.33
	339.609	2.945		221.91
		0.589		52.48
		0.118		32.99

 896-0819				
896-0819	124.219	uM	-16.20	
	12.422		70.03	
402.516	2.484		165.79	
	0.497		82.61	
	0.099		49.06	
 896-0853				
896-0853	157.546	uM	-27.08	
	15.756		75.38	
317.367	3.151		208.69	
	0.630		33.08	
	0.126		32.63	
 896-0921				
896-0921	174.583	uM	-19.58	
	17.458		44.07	
286.397	3.492		103.23	
	0.698		54.02	
	0.140		23.86	



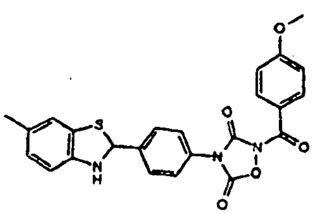
896-0936

896-0936	184.314	uM	-16.20
	18.431		153.61
271.276	3.686		184.53
	0.737		79.16
	0.147		32.61



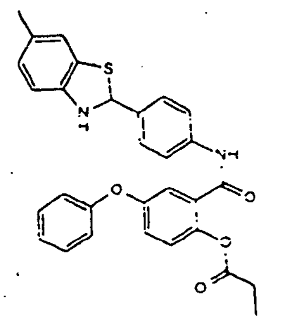
896-0969

896-0969	103.798	uM	-1.73
	10.380		102.48
461.703	2.076		61.61
	0.415		63.56
	0.083		48.27



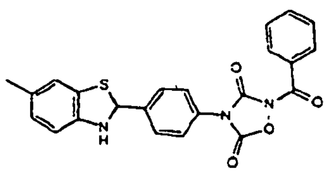
896-1201

896-1201	108.343	uM	-45.70
	10.834		92.57
461.496	2.167		191.83
	0.433		47.22
	0.087		58.25



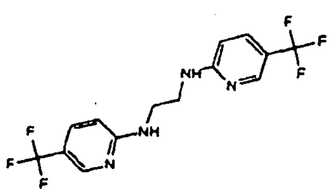
896-1301

896-1301	97.922	uM	-24.32
	9.792		102.49
510.612	1.958		139.28
	0.392		97.89
	0.078		23.45



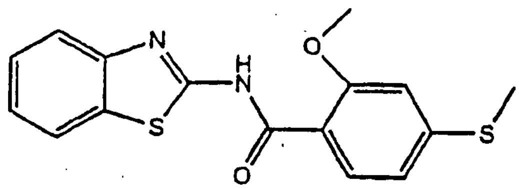
896-1349

896-1349	115.883	uM	-39.92
	11.588		55.08
431.47	2.318		122.68
	0.464		67.25
	0.093		3.39



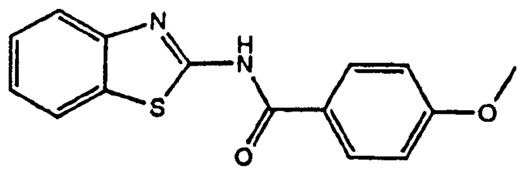
896-1362

896-1362	142.749	uM	1,073.91
	14.275		1,082.17
360.266	2.855		884.71
	0.571		-9.82
	0.114		-20.37



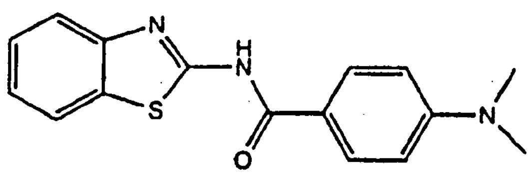
Max : 215 %
EC50 : < 0.8 nM

59-0072



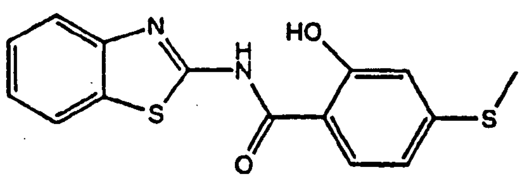
Max : 121 %
EC50 : 30 nM

59-0102



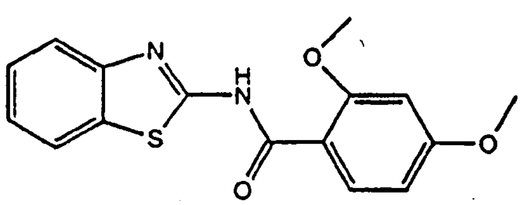
Max : 214 %
EC50 : 200 nM

59-0070



Max : 54 %
EC50 : 2 μM

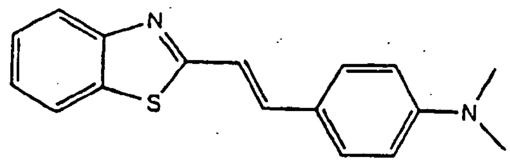
59-0144



Max : 340 %
EC50 : < 0.8 nM

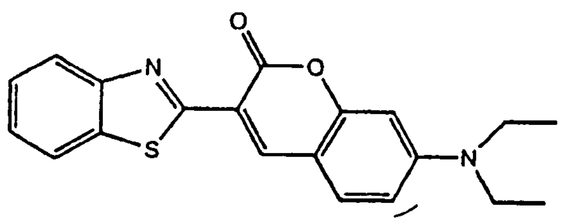
59-0147

FIG. 5A

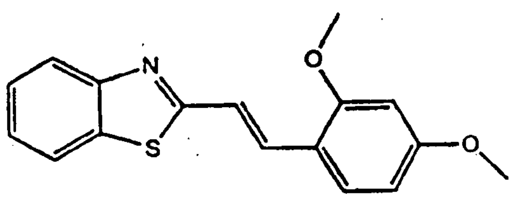


Max : 285 %
EC50 : 3 nM

59-0099



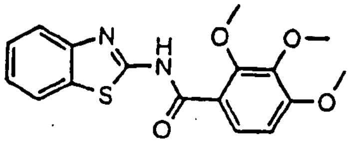
Max : 269 %
EC50 : < 0.8 nM



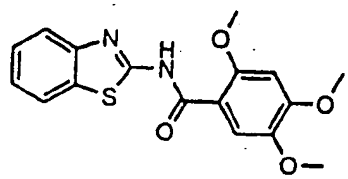
Max : 200 %
EC50 : 30 nM

59-0210

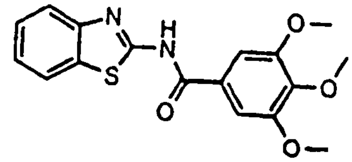
FIG. 5B



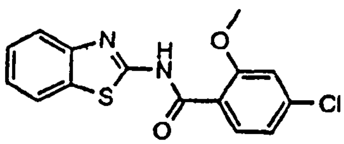
59-0192
Max : 155 %
EC50 : 20 nM



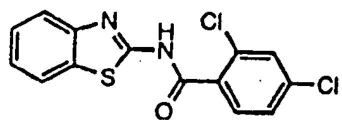
59-0193
Max : 95 %
EC50 : 30 nM



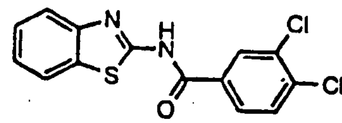
59-0194
Inactive



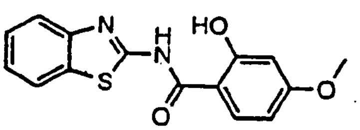
59-0195
Max : 155 %
EC50 : 20 nM



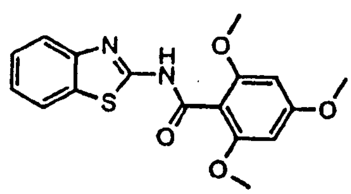
59-0196
Inactive



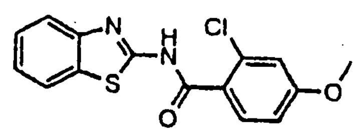
59-0197
Max : 162 %
EC50 : 150 nM



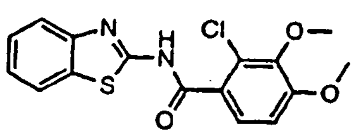
59-0202
Max : 155 %
EC50 : 150 nM



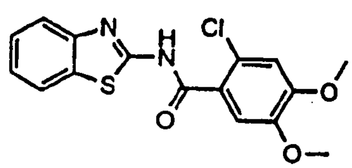
59-0204
Max : 70 %
EC50 : 50 nM



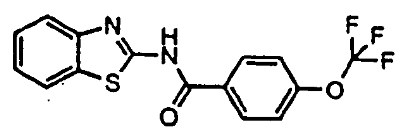
59-0205
Max : 250 %
EC50 : < 0.8 nM



59-0206
Max : 150 %
EC50 : 20 nM

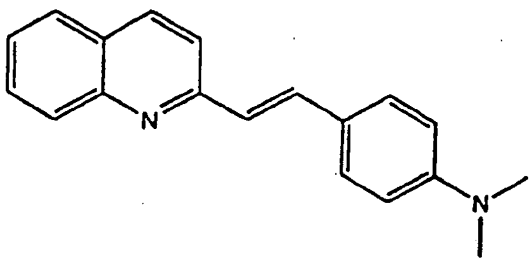


59-0207
Max : 50 %
EC50 : 100 nM

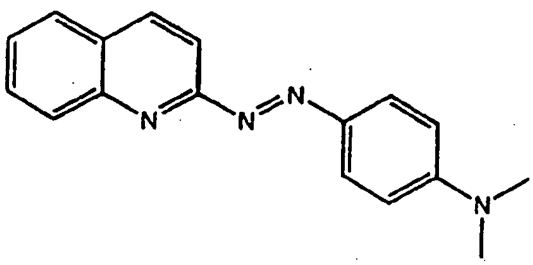


59-0208
Max : 85 %
EC50 : 1 uM

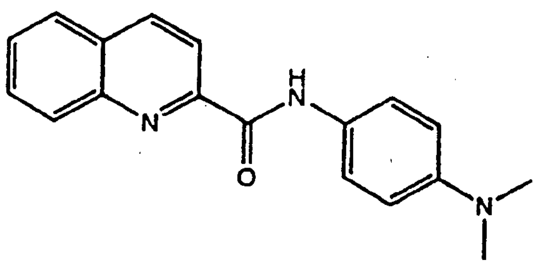
FIG. 5C



50-0197
Max : 245 %
EC50 : 3 nM



59-0078
Max : 380 %
EC50 : 1 nM



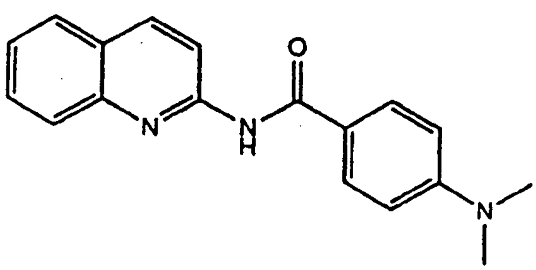
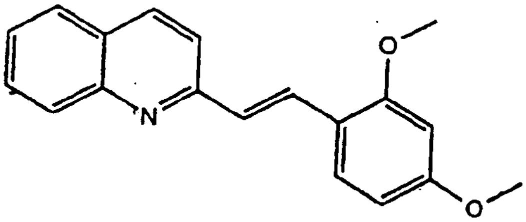
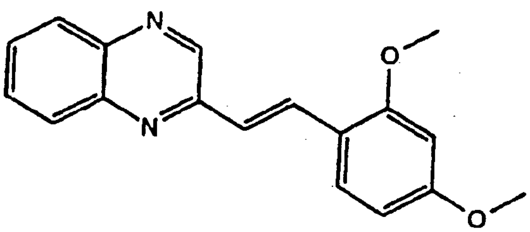


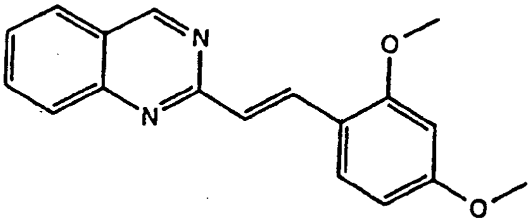
FIG. 6A



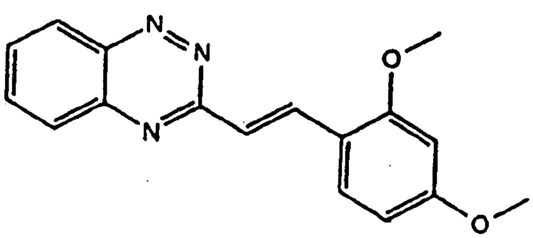
59-0199
Max : 170 %
EC50 : 100 nM



59-0203
Max : 275 %
EC50 : < 1 nM

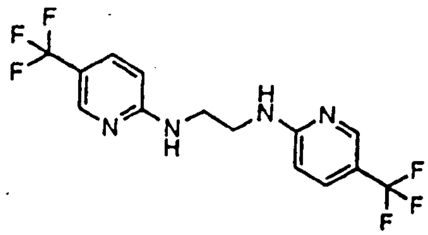


59-0286
Max : 160 %
EC50 : 300 nM



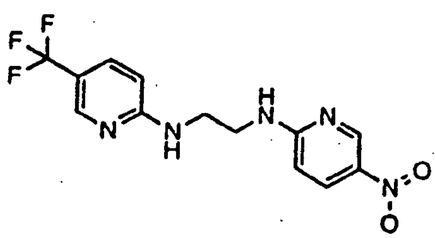
59-0285
Max : 200 %
EC50 : 30 nM

FIG. 6B



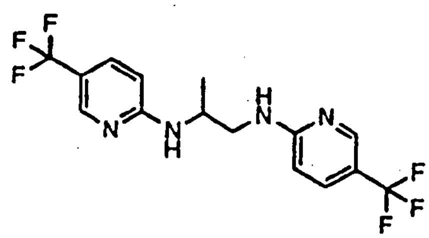
59-0145

Max : 300 %
EC50 : 0.5 uM



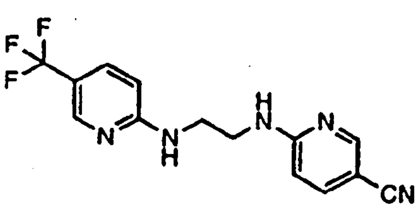
59-0450

Max : 270 %
EC50 : 5 uM



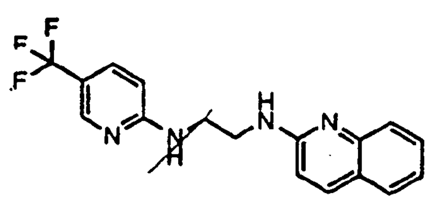
59-0459

Max : 180 %
EC50 : 5 uM



59-0483

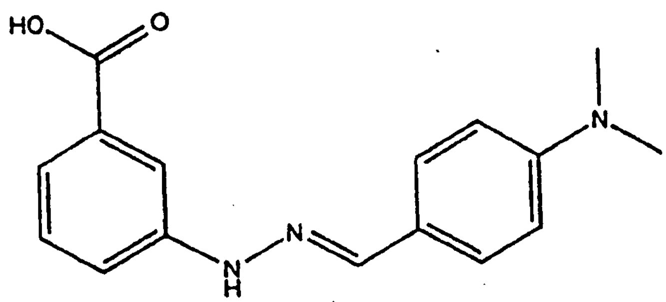
Max : 260 %
EC50 : 3 uM



59-0480

Max : 180 %
EC50 : 5 uM

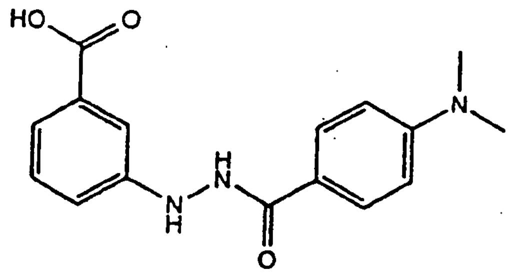
FIG. 7



59-0045

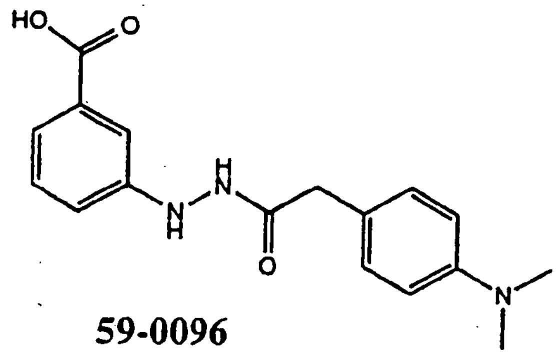
ECSO = 5nM

FIG. 8A



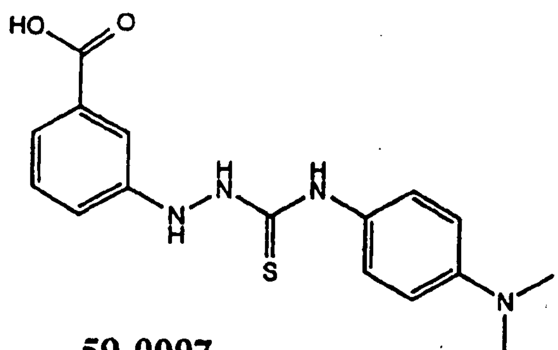
59-0095

Max : 48 %
EC50 : 30 μM



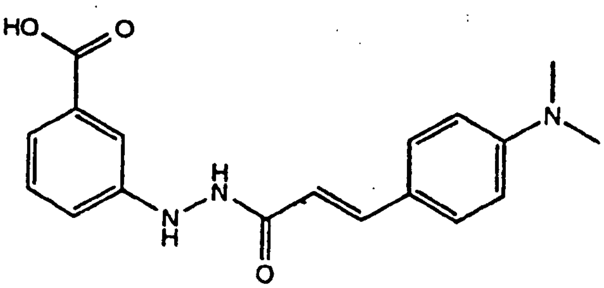
59-0096

Max : 413 %
EC50 : 93 nM



59-0097

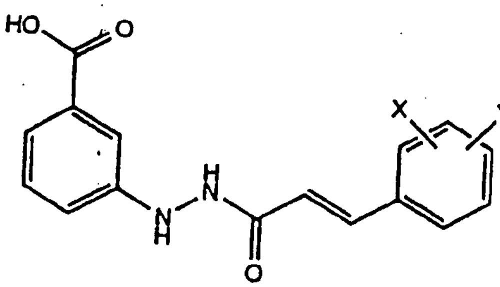
Max : 202 %
EC50 : 100 nM



59-0098

Max : 222 %
EC50 : 20 nM

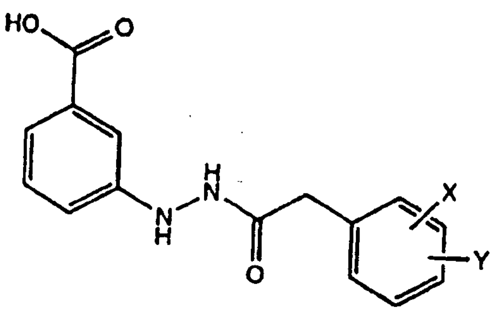
FIG. 8B



X, Y = F, Cl, OMe

< 50 % max @ 100 uM

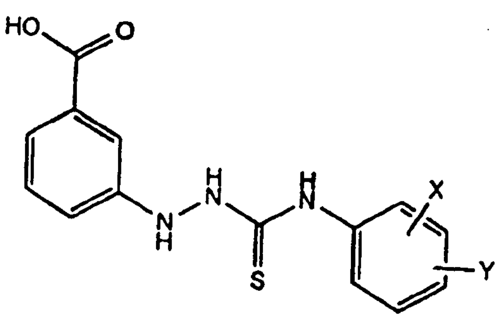
59-0098 Analogs



X, Y = F, Cl, OMe

< 50 % max @ 100 uM

59-0096 Analogs



X, Y = F, Cl, OMe

< 50 % max @ 100 uM

59-0097 Analogs

FIG. 8C

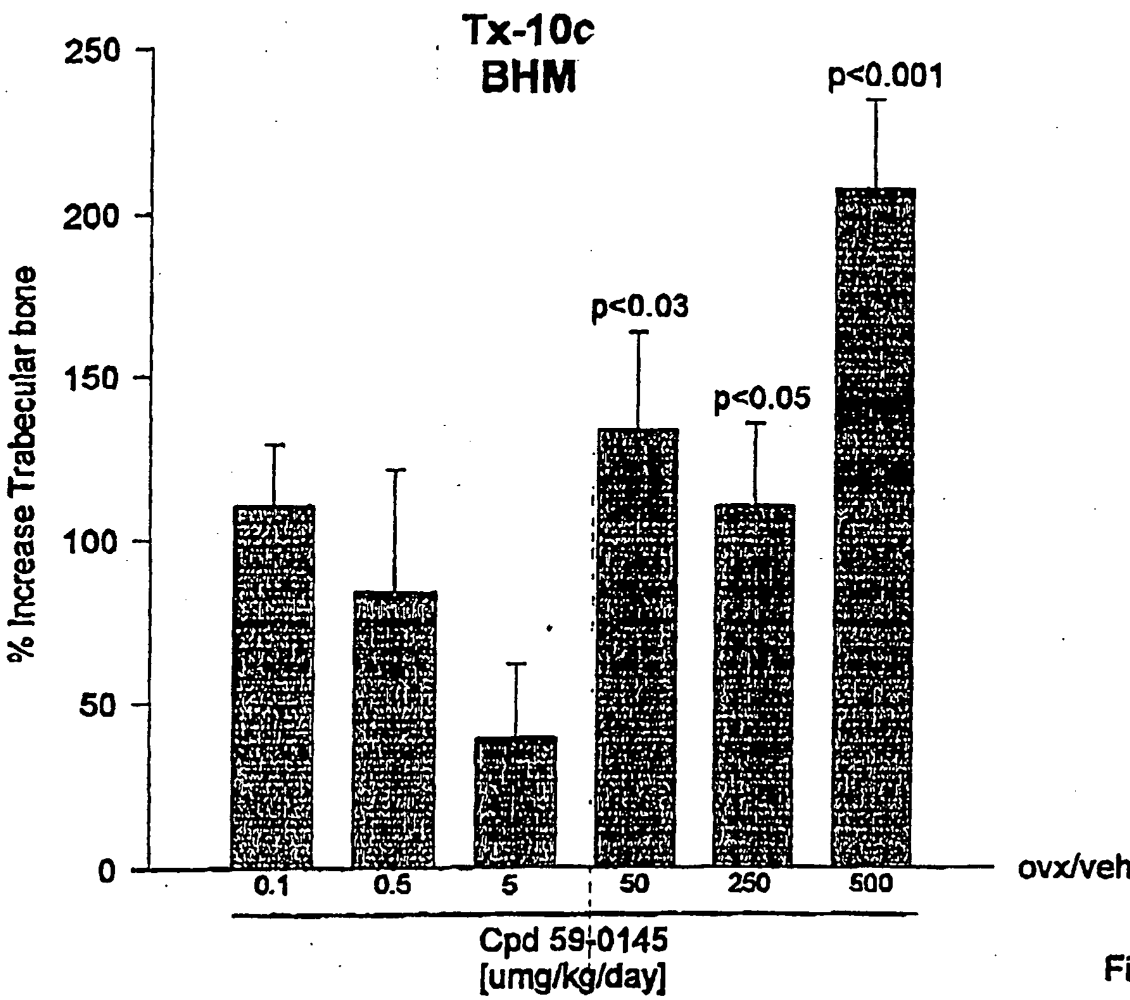
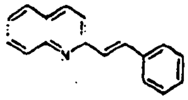
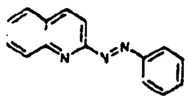
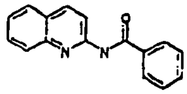
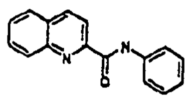
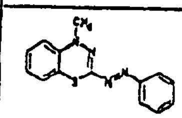
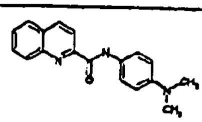
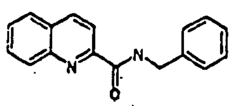
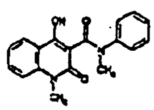
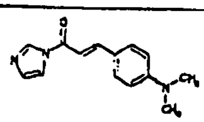
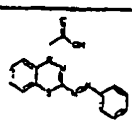
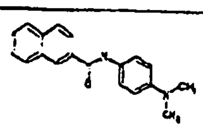
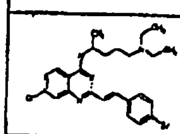


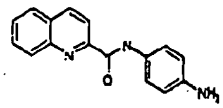
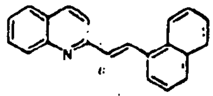
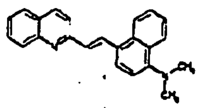
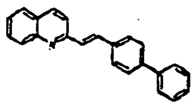
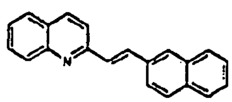
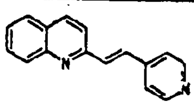
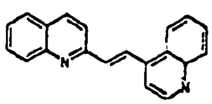
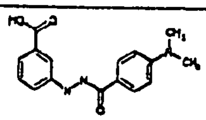
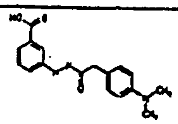
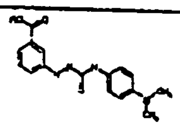
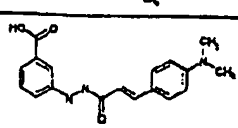
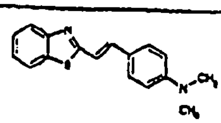
Fig 1Y

% Increase of trabecular bone over the ovx/vehicle group

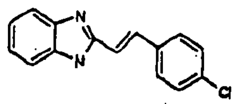
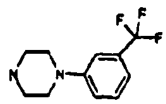
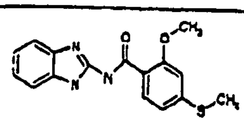
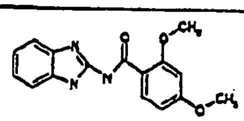
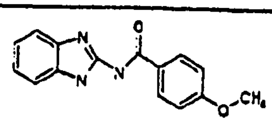
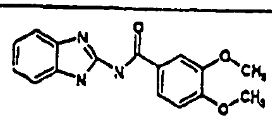
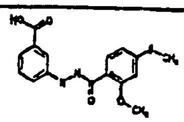
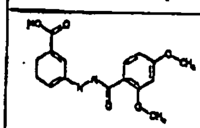
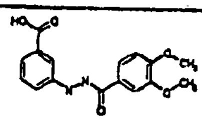
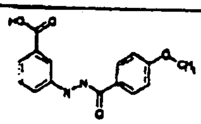
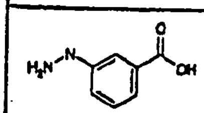
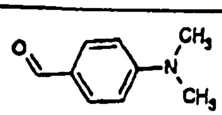
nand2

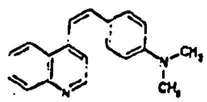
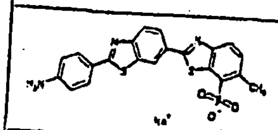
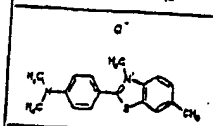
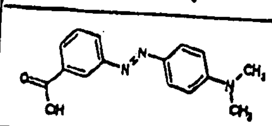
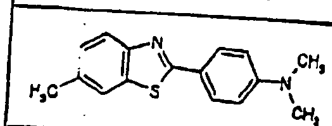
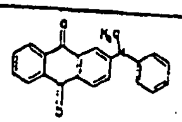
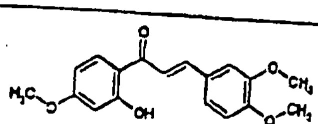
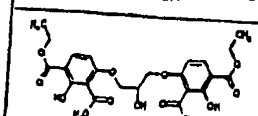
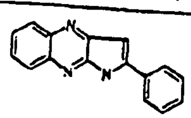
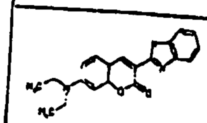
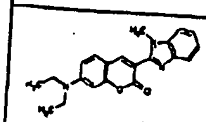
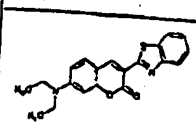
	59-0031	231.3	
	59-0030	233.275	
	59-0032	248.287	
	59-0033	248.287	
	59-0034	268.343	
	59-0035	291.356	
	59-0036	262.314	
	59-0037	308	
	59-0038	241.295	
	59-0039	312.352	
	59-0040	290.368	
	59-0041	501.902	

nand2

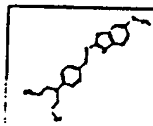
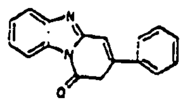
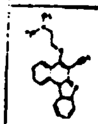
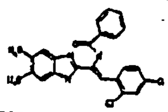
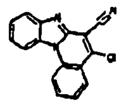
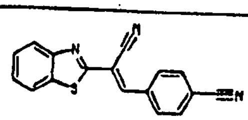
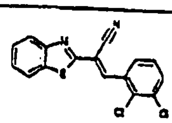
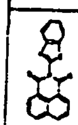
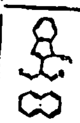
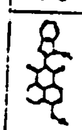
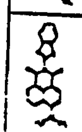
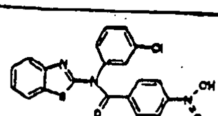
	59-0088	263.299	
	59-0089	281.357	
	59-0090	324.425	
	59-0091	307.394	
	59-0092	281.357	
	59-0093	232.285	
	59-0094	282.345	
	59-0095	299.328	
	59-0096	313.355	
	59-0097	330.41	
	59-0098	325.368	
	59-0099	280.393	

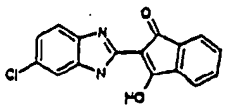
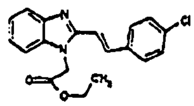
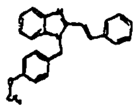
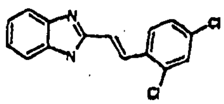
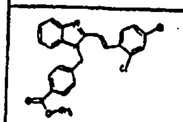
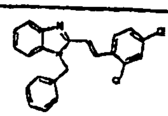
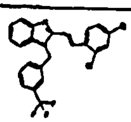
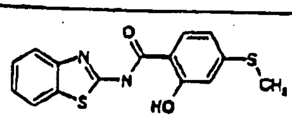
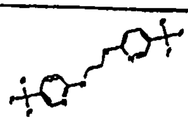
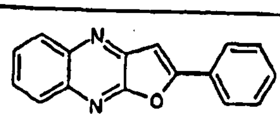
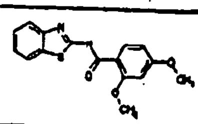
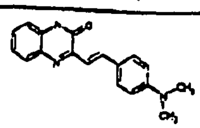
nand2

	59-0100	254.719	
	59-0101	230.232	
	59-0103	313.379	
	59-0104	297.312	
	59-0105	267.287	
	59-0106	297.312	
	59-0107	332.378	
	59-0108	316.311	
	59-0109	316.311	
	59-0110	286.286	
	59-0111	152.152	
	59-0112	149.192	

	59-0113	274.365	
	59-0114	475.548	
	59-0115	318.87	
	59-0116	269.302	
	59-0117	268.382	
	59-0118	313.354	
	59-0119	314.335	
	59-0120	504.485	
	59-0121	245.284	
	59-0122	333.389	
	59-0123	347.416	
	59-0124	350.44	

nand2

	59-0125	372.447		
	59-0126	260.295		
	59-0127	329.405		
	59-0128	436.34		
	59-0129	277.713		
	59-0130	287.345		
	59-0131	331.225		
	59-0132	313.315		
	59-0133	327.342		
	59-0134	357.367		
	59-0135	356.383		
	59-0136	411.868		

	59-0137	296.712	
	59-0138	340.808	
	59-0139	340.424	
	59-0140	289.164	
	59-0141	437.324	
	59-0142	379.288	
	59-0143	447.285	
	59-0144	316.404	
	59-0145	350.265	
	59-0146	246.268	
	59-0147	314.364	
	59-0148	291.352	

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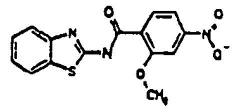
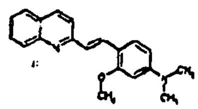
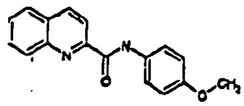
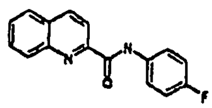
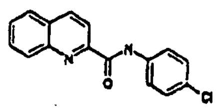
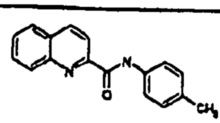
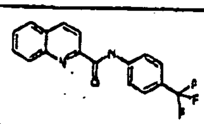
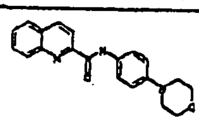
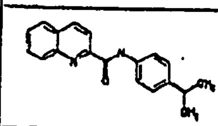
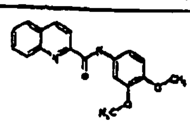
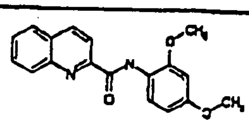
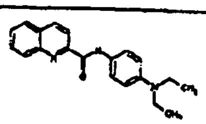
	59-0149	329.335	
	59-0150	304.391	
	59-0151	278.31	
	59-0152	266.274	
	59-0153	282.729	
	59-0154	262.311	
	59-0155	316.281	
	59-0156	333.389	
	59-0157	290.364	
	59-0158	308.335	
	59-0159	308.335	
	59-0160	319.406	

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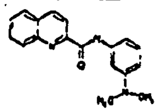
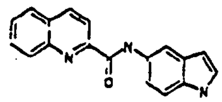
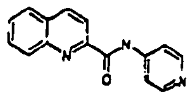
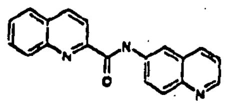
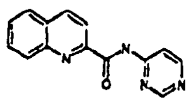
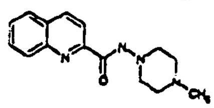
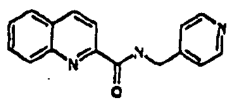
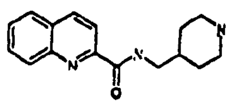
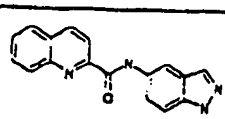
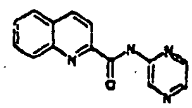
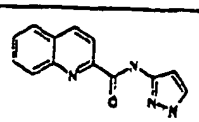
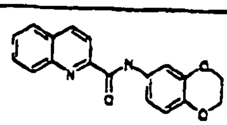
	59-0161		281.352	
	59-0162		287.321	
	59-0163		249.272	
	59-0164		299.332	
	59-0165		250.26	
	59-0166		270.334	
	59-0167		263.299	
	59-0168		269.346	
	59-0169		288.309	
	59-0170		250.26	
	59-0171		238.249	
	59-0172		306.32	

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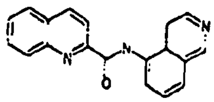
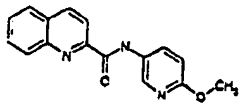
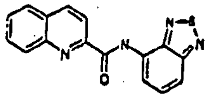
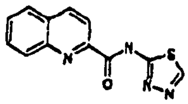
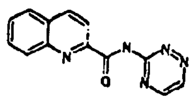
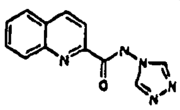
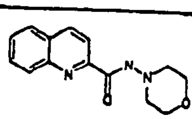
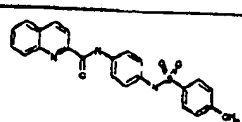
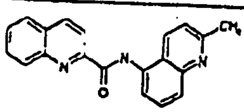
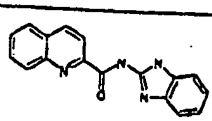
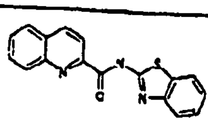
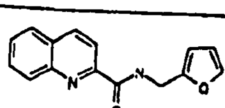
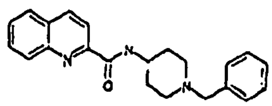
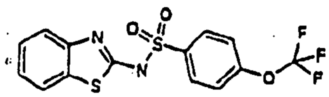
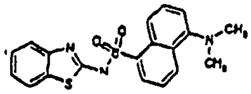
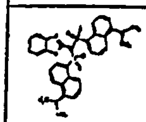
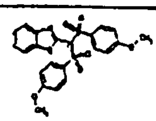
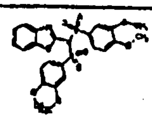
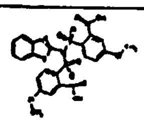
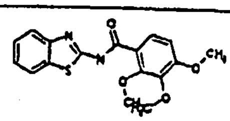
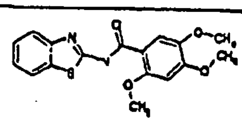
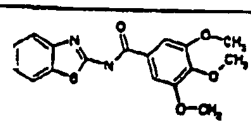
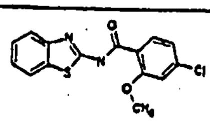
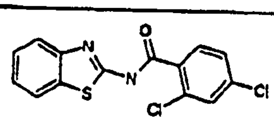
	59-0173	299.332	
	59-0174	279.298	
	59-0175	306.348	
	59-0176	256.288	
	59-0177	251.248	
	59-0178	239.237	
	59-0179	257.292	
	59-0180	417.487	
	59-0181	313.358	
	59-0182	288.309	
	59-0183	305.36	
	59-0184	252.272	

	59-0185	345.444	
	59-0186	374.382	
	59-0187	389.494	
	59-0188	616.784	
	59-0189	490.579	
	59-0190	550.631	
	59-0191	584.605	
	59-0192	344.389	
	59-0193	344.389	
	59-0194	344.389	
	59-0195	318.783	
	59-0196	323.202	

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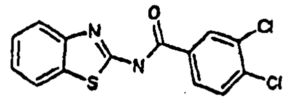
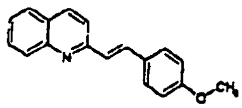
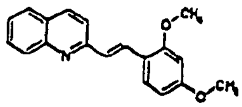
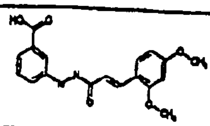
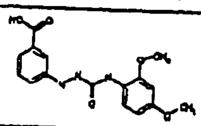
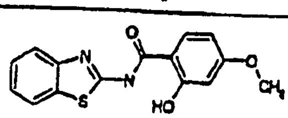
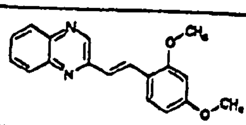
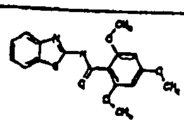
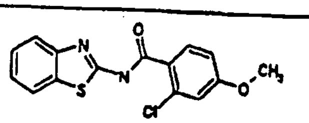
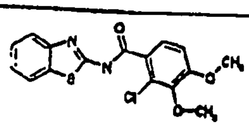
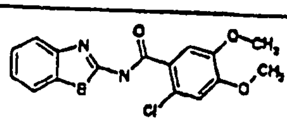
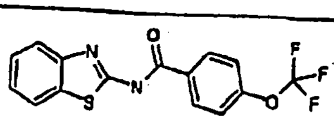
	59-0197	323.202	
	59-0198	261.323	
	59-0199	291.348	
	59-0200	342.349	
	59-0201	331.326	
	59-0202	300.337	
	59-0203	292.336	
	59-0204	344.389	
	59-0205	318.783	
	59-0206	348.809	
	59-0207	348.809	
	59-0208	338.308	

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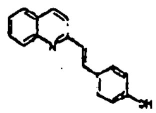
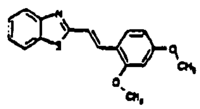
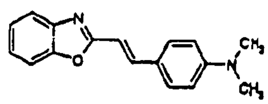
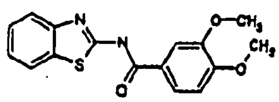
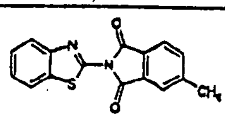
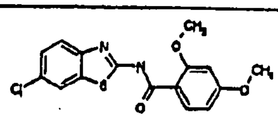
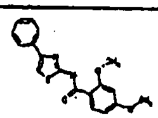
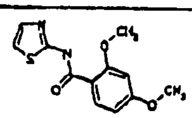
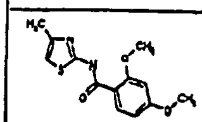
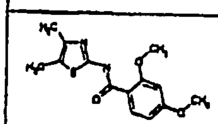
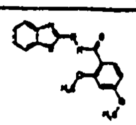
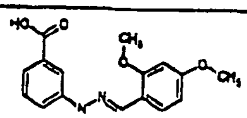
	59-0209	247.296	
	59-0210	297.376	
	59-0211	264.326	
	59-0212	314.364	
	59-0213	294.333	
	59-0214	348.809	
	59-0215	340.401	
	59-0216	264.304	
	59-0217	278.331	
	59-0218	292.357	
	59-0219	329.379	
	59-0220	300.312	

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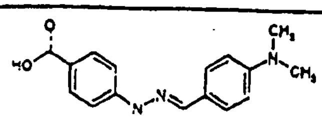
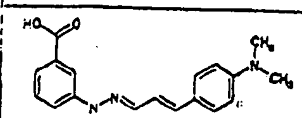
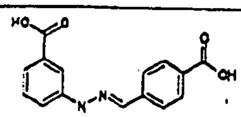
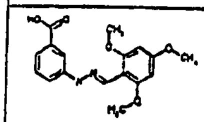
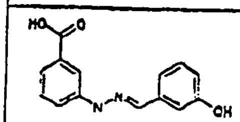
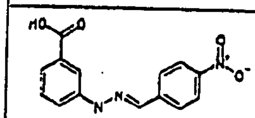
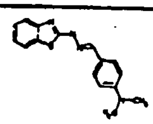
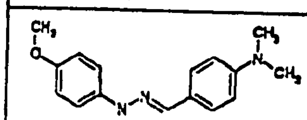
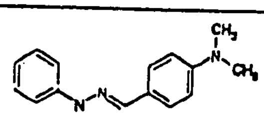
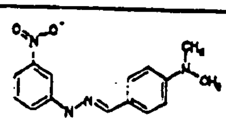
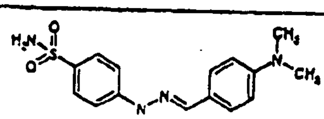
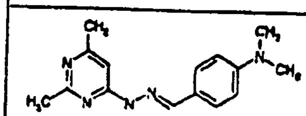
	59-0221	283.329	
	59-0222	309.367	
	59-0223	284.27	
	59-0224	330.338	
	59-0225	256.26	
	59-0226	285.258	
	59-0227	296.398	
	59-0228	269.346	
	59-0229	239.32	
	59-0230	284.317	
	59-0231	318.399	
	59-0232	269.35	

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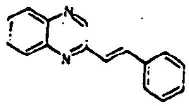
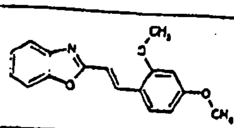
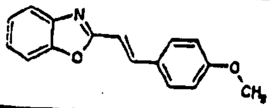
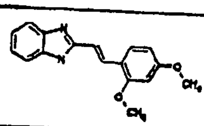
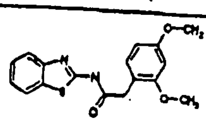
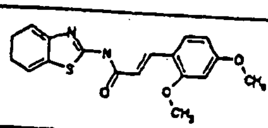
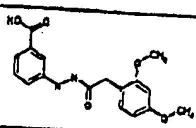
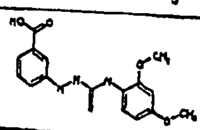
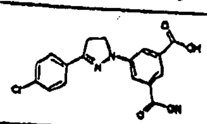
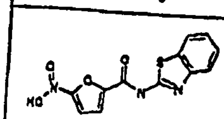
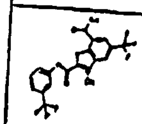
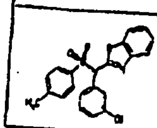
	59-0233	232.285	
	59-0234	281.31	
	59-0235	251.284	
	59-0236	280.325	
	59-0237	328.39	
	59-0238	340.401	
	59-0239	330.338	
	59-0240	347.393	
	59-0241	344.753	
	59-0242	291.286	
	59-0243	455.334	
	59-0244	414.935	

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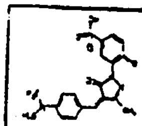
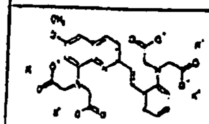
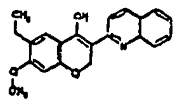
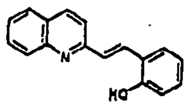
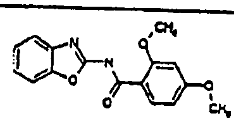
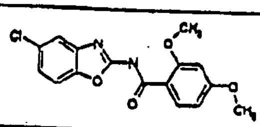
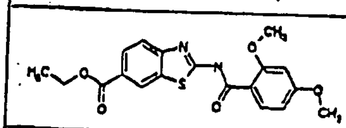
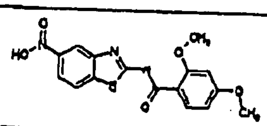
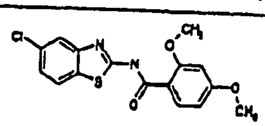
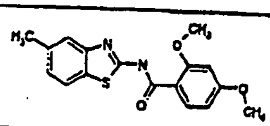
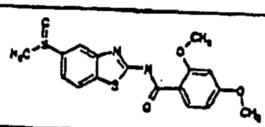
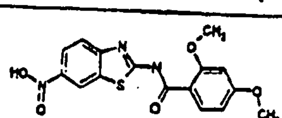
	59-0245	419.887	
	59-0246	675.856	
	59-0247	333.385	
	59-0248	247.296	
	59-0249	298.297	
	59-0250	332.742	
	59-0251	386.426	
	59-0252	361.376	
	59-0253	348.809	
	59-0254	328.39	
	59-0255	376.455	
	59-0256	361.376	

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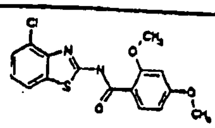
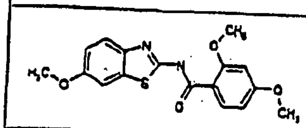
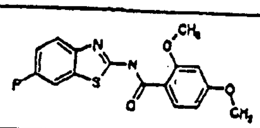
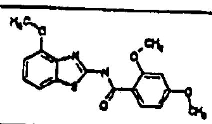
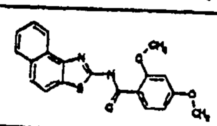
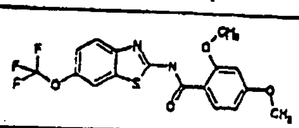
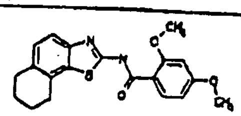
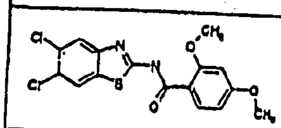
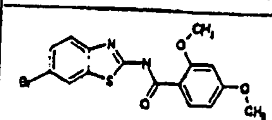
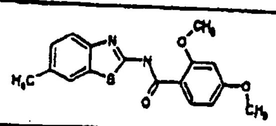
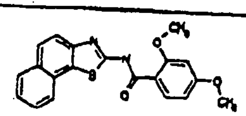
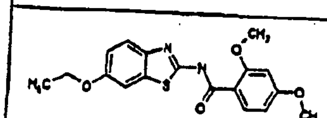
	59-0257	348.809	
	59-0258	344.389	
	59-0259	332.354	
	59-0260	344.389	
	59-0261	364.423	
	59-0262	398.36	
	59-0263	368.455	
	59-0264	383.254	
	59-0265	393.26	
	59-0266	328.39	
	59-0267	364.423	
	59-0268	358.416	

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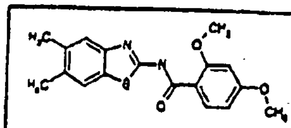
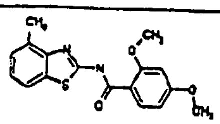
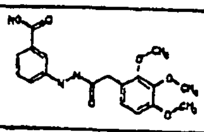
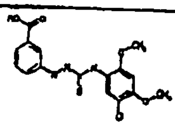
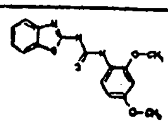
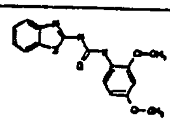
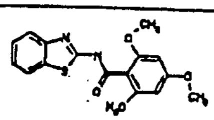
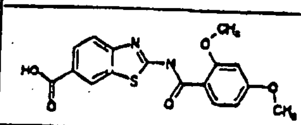
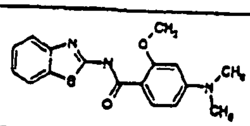
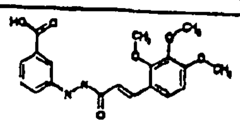
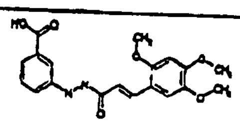
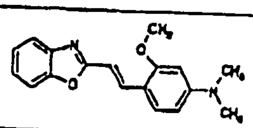
	59-0269	342.417	
	59-0270	328.39	
	59-0271	360.364	
	59-0272	381.838	
	59-0273	345.445	
	59-0274	329.379	
	59-0275	328.39	
	59-0276	358.373	
	59-0279	327.406	
	59-0277	372.375	
	59-0278	372.375	
	59-0280	294.352	

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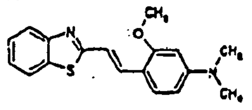
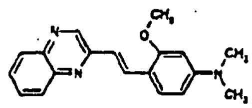
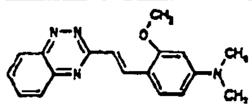
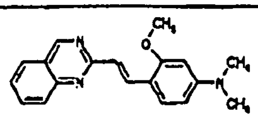
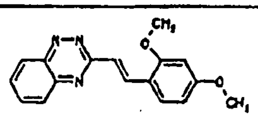
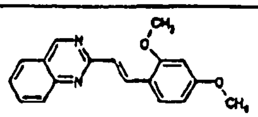
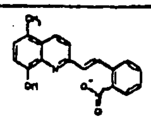
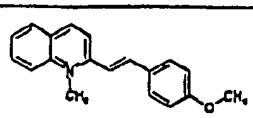
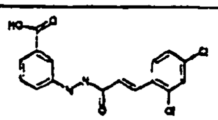
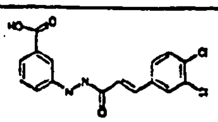
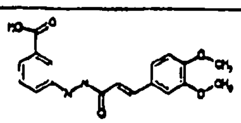
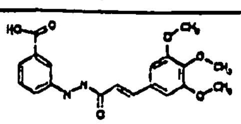
	59-0281	310.419
	59-0282	305.379
	59-0283	306.367
	59-0284	305.379
	59-0285	293.324
	59-0286	292.336
	59-0287	306.32
	59-0288	276.357
	59-0289	351.188
	59-0290	351.188
	59-0291	342.349
	59-0292	372.375

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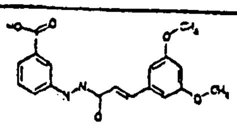
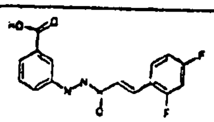
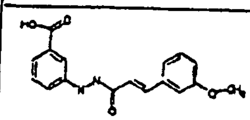
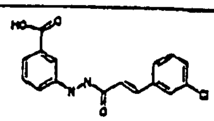
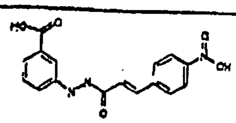
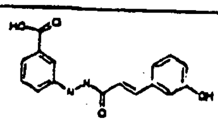
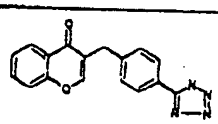
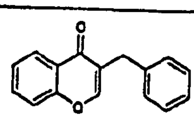
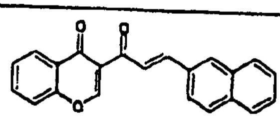
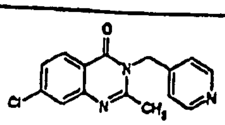
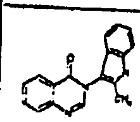
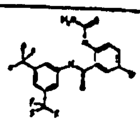
	59-0293	342.349	
	59-0294	318.278	
	59-0295	312.323	
	59-0296	316.743	
	59-0297	329.31	
	59-0298	298.297	
	59-0299	304.308	
	59-0300	236.269	
	59-0301	326.35	
	59-0302	285.733	
	59-0303	275.31	
	59-0304	469.178	

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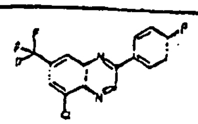
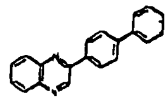
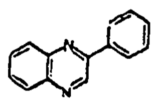
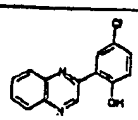
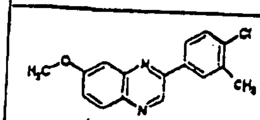
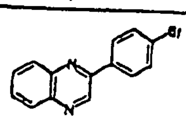
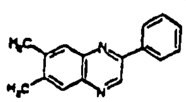
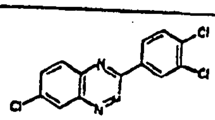
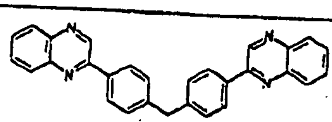
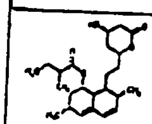
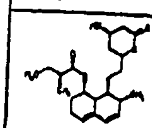
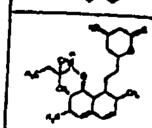
	59-0318	326.6791	
	59-0319	282.345	
	59-0320	206.247	
	59-0321	256.691	
	59-0322	284.745	
	59-0923	285.143	
	59-0324	234.301	
	59-0312	309.582	
	59-0325	424.505	
	59-0326	404.543	
	59-0327	390.517	
	59-0328	418.57	

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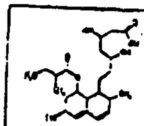
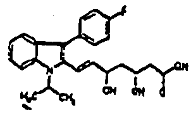
	59-0329	424.53	
	59-0330	411.47	

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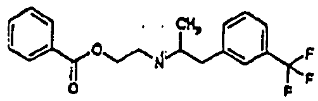
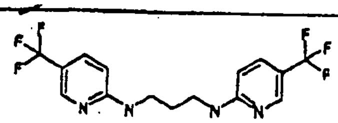
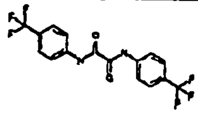
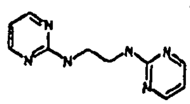
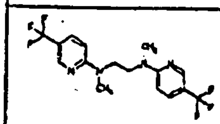
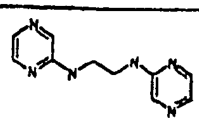
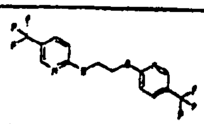
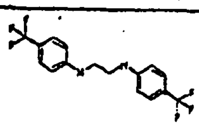
	!59-0357	351.366	

	59-0361	364.292	
	59-0362	376.255	
	59-0363	216.247	
	59-0364	378.318	
	59-0365	216.247	
	59-0366	384.367	
	59-0367	348.289	

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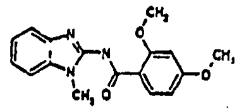
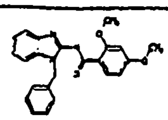
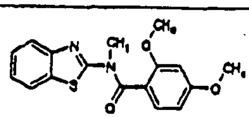
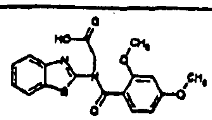
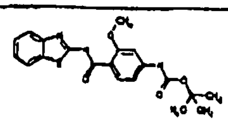
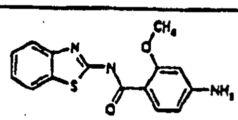
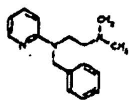
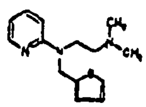
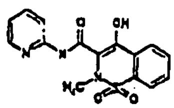
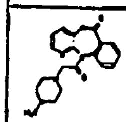
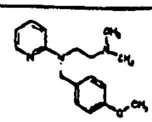
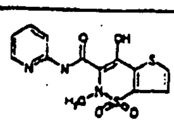
	59-0368	311.339	
	59-0369	387.437	
	59-0370	328.39	
	59-0371	372.399	
	59-0372	399.469	
	59-0373	299.353	
	59-0374	255.363	
	59-0375	261.391	
	59-0376	331.351	
	59-0377	351.408	
	59-0378	285.389	
	59-0379	337.379	

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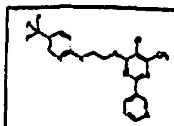
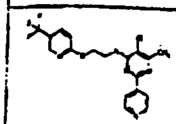
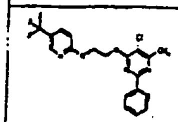
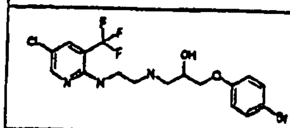
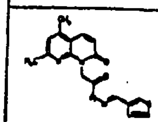
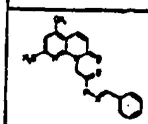
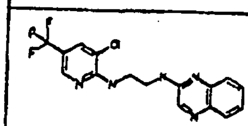
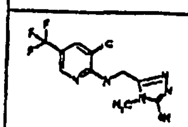
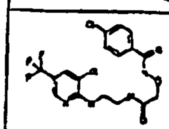
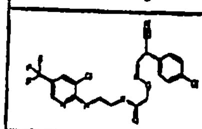
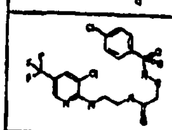
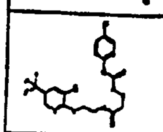
	59-0380	408.813	
	59-0381	408.813	
	59-0382	408.813	
	59-0383	468.699	
	59-0384	340.405	
	59-0385	334.377	
	59-0386	367.761	
	59-0387	323.729	
	59-0388	451.23	
	59-0389	474.268	
	59-0390	487.284	
	59-0391	466.245	

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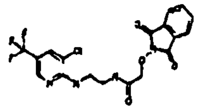
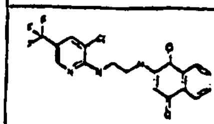
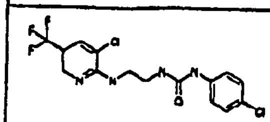
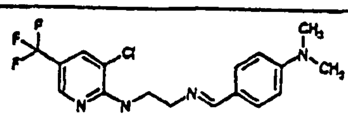
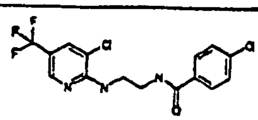
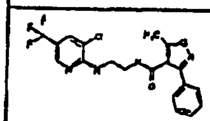
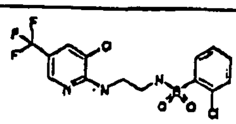
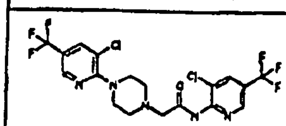
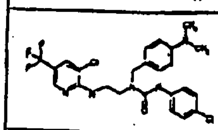
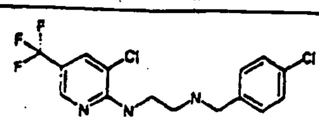
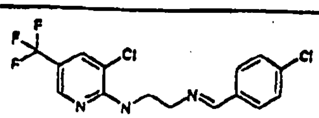
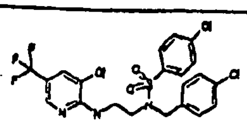
	59-0392	442.78	
	59-0393	395.767	
	59-0394	393.195	
	59-0395	370.804	
	59-0396	378.18	
	59-0397	424.808	
	59-0398	414.234	
	59-0399	502.245	
	59-0400	526.388	
	59-0401	364.197	
	59-0402	362.181	
	59-0403	538.803	

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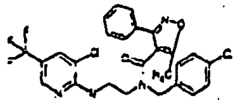
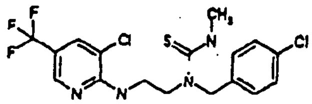
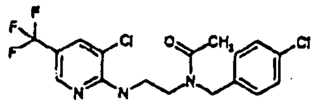
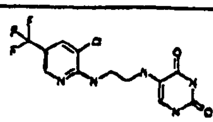
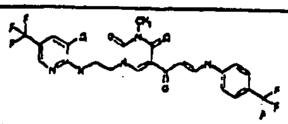
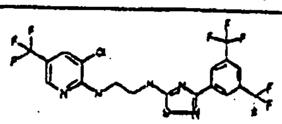
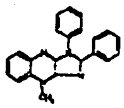
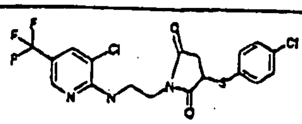
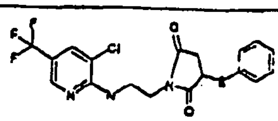
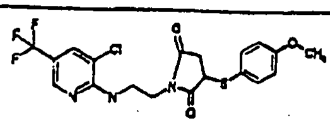
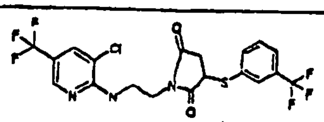
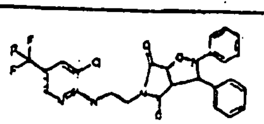
	59-0404	549.378	
	59-0405	437.315	
	59-0406	406.233	
	59-0407	349.699	
	59-0408	561.868	
	59-0409	535.821	
	59-0410	340.428	
	59-0411	464.294	
	59-0412	429.849	
	59-0413	459.874	
	59-0414	497.846	
	59-0415	516.905	

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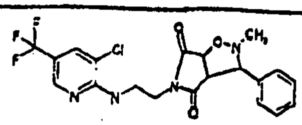
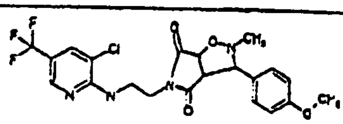
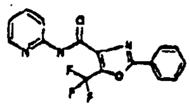
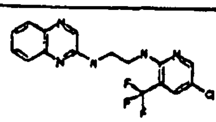
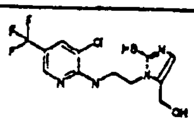
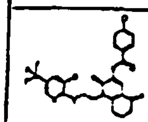
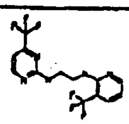
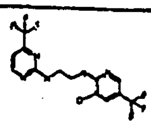
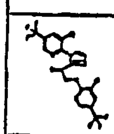
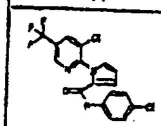
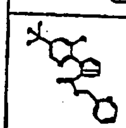
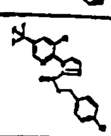
	59-0416	454.834	
	59-0417	484.86	
	59-0418	333.268	
	59-0419	367.761	
	59-0420	352.767	
	59-0421	539.339	
	59-0422	351.253	
	59-0423	385.698	
	59-0424	484.186	
	59-0425	400.186	
	59-0426	380.756	
	59-0427	414.213	

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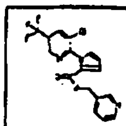
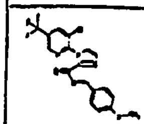
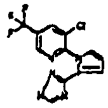
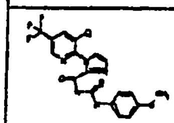
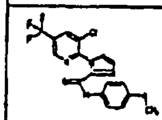
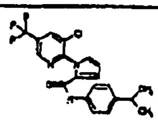
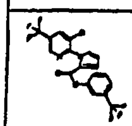
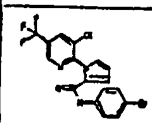
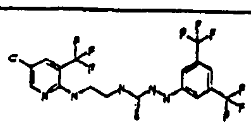
	59-0428	380.756	
	59-0429	409.793	
	59-0430	313.669	
	59-0431	454.859	
	59-0432	395.767	
	59-0433	407.821	
	59-0435	433.738	
	59-0436	444.637	
	59-0439	525.826	

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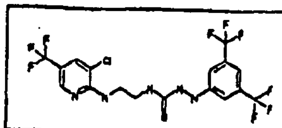
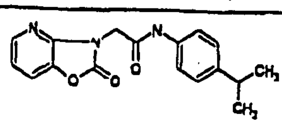
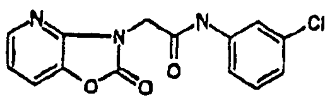
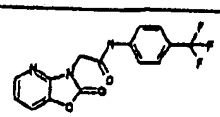
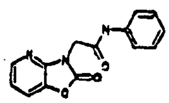
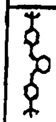
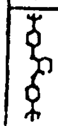
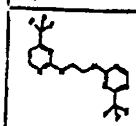
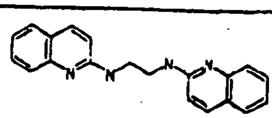
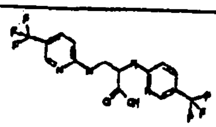
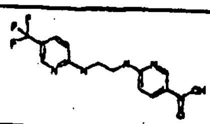
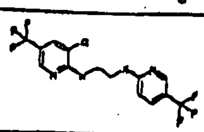
	59-0440	525.826	
	59-0441	311.339	
	59-0442	303.704	
	59-0443	337.256	
	59-0444	269.259	
	59-0445	404.356	
	59-0446	404.356	
	59-0447	352.241	
	59-0448	314.39	
	59-0449	394.274	
	59-0450	329.281	
	59-0451	384.71	

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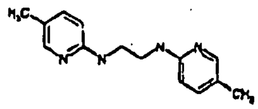
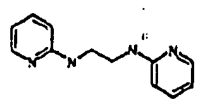
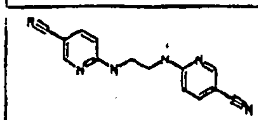
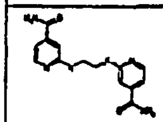
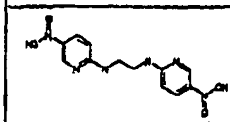
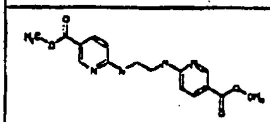
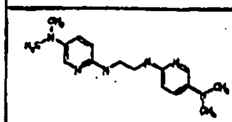
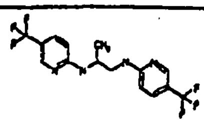
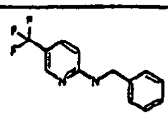
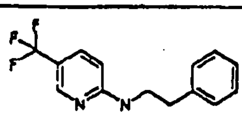
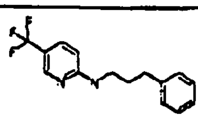
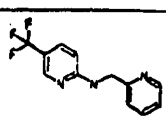
	59-0452	242.324	
	59-0453	214.271	
	59-0454	264.291	
	59-0455	300.32	
	59-0456	308.296	
	59-0457	330.342	
	59-0458	300.408	
	59-0459	364.292	
	59-0460	252.238	
	59-0461	266.265	
	59-0462	280.292	
	59-0463	253.226	

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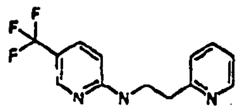
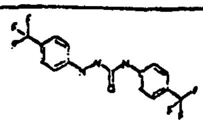
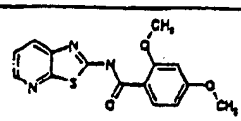
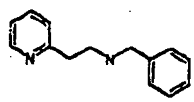
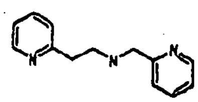
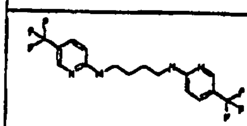
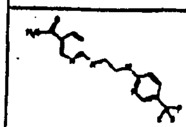
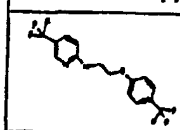
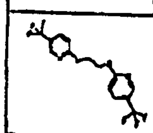
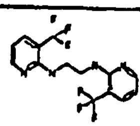
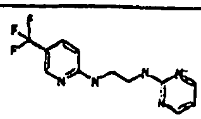
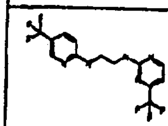
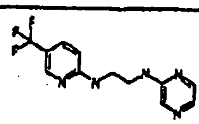
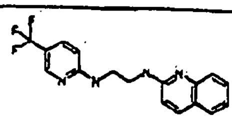
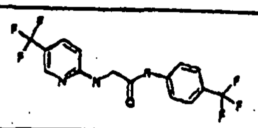
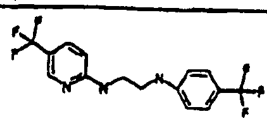
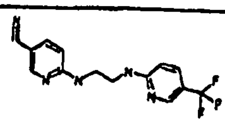
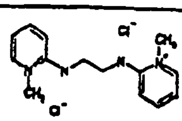
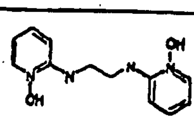
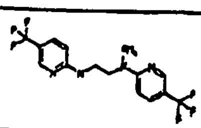
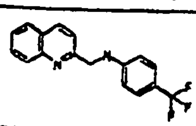
	59-0464	267.253	
	59-0465	363.26	
	59-0466	315.352	
	59-0467	212.294	
	59-0468	213.283	
	59-0469	378.318	
	59-0470	325.293	
	59-0471	350.261	
	59-0472	351.249	

	59-0476	350.265	
	59-0477	283.256	
	59-0478	351.253	
	59-0479	283.256	
	59-0480	332.328	
	59-0481	363.26	
	59-0482	349.277	
	59-0483	307.278	
	59-0484	315.246	
	59-0485	250.3	
	59-0486	364.292	
	59-0487	302.298	

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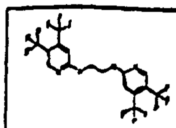
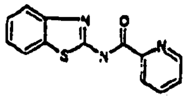
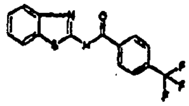
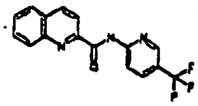
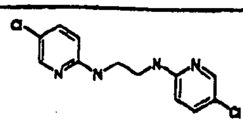
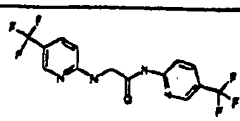
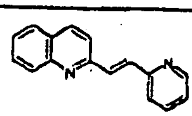
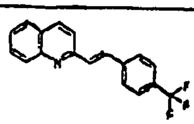
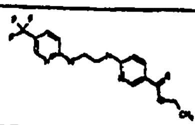
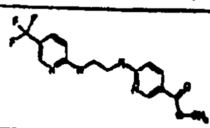
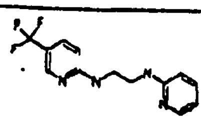
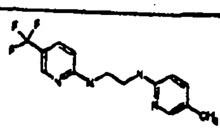
	59-0488	486.259	
	59-0489	255.3	
	59-0490	322.309	
	59-0491	317.269	
	59-0492	283.161	
	59-0493	364.248	
	59-0494	232.285	
	59-0495	299.294	
	59-0496	354.33	
	59-0497	340.303	
	59-0498	282.268	
	59-0499	296.294	

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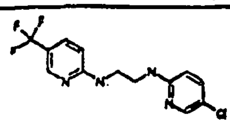	59-0500	316.713	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/18864

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS--structure
APS--diaryl, bone, osteo?, BMP
DIALOG--diaryl, bone, osteo?, BMP

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,441,964 A (BRYANT et al.) 15 August 1995, see entire document.	1-2, 5-28, 55-56
Y	US 5,523,309 A (BRYANT et al.) 04 June 1996, see entire document, especially claim 8.	1-2, 5-28, 55-56
Y,P	US 5,622,974 A (MUEHL) 22 April 1997, see entire document, especially claim 5.	1-2, 5-28, 55-56
Y	WO 93/10113 A1 (TEIKOKU HORMONE MFG. CO., LTD.) 27 May 1993, see entire document.	1-2, 5-28, 55-56
Y	WO 95/10513 A1 (PFIZER INC.) 20 April 1995, see entire document, especially claim 20.	1-2, 5-30, 55-56
Y	US 5,280,040 A (LABROO et al.) 18 January 1994, see entire document.	1-4, 31-43, 55-56

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 JANUARY 1998	26 FEB 1998

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	CELIA CHANG
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chem. abstr. Vol. 127, abstract No. 127:17703, PETRIE et al. 'Preparation of (hetero) aromatic compounds for treating bone deficit conditions', WO-97/15308 (Eng.).	1-4, 31-43, 55-56
Y	Chem. abstr. Vol. 107, abst. No. 107:109578, WATTS et al. 'Studies on the ligand specificity and potential identity of microsomal antiestrogen-binding sites', Mol. Pharmocol. 1987, 31(5), 541-51.	1-2, 50-56
Y	Chem. abstr. Vol. 108, abstract No. 108:69162, JORDAN et al. 'Effects of antiestrogens on bone in castrated and intact female rats', Breast Cancer Res. Treat. 1987, 10(1), 31-5.	1-2, 50-56
Y	Chem. abstr. Vol. 115, abstract No. 115:8533, SCHWARZ et al. '1,2-diphenyl-1-pyridybut-1-enes - potential antiestrogens. part 1. synthesis' Arch. Pharm. 1991, 324(4), 223-9.	1-2, 44-49, 55-56
Y	NEELAM et al. Structure-activity relationship of antiestrogens: A study using triarylbutenone, benzofuran and triayrlfuran analogues as models for triarylethylenes and triarylpropenones. J. Med. chem. 1989, Vol. 32, pages 1700-1707, see entire article.	1-2, 50-56
Y	VON ANGERER et al. Studies on heterocycle-based pure estrogen antagonists. Ann. N. Y. Academy Sciences. 1995, Vol. 761, pages 176-191, see especially pages 178-180.	1-2, 5-28, 55-56

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/18864

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.